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## CANCER OF THE RECTUM\*

An Analysis of Cases Occurring in Connecticut during 1935-1945†

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IN 1935 a plan was inaugurated in Connecticut whereby duplicate copies of hospital records of patients with cancer were made available to the Division of Cancer Research of the Connecticut Department of Health. This was a joint undertaking sponsored by the Tumor Committee and the Association of Tumor Clinics of the Connecticut State Medical Society, the general hospitals of the state, and the State Department of Health. As a result of fortuitous co-operation, complete data on over 35,000 cases of cancer have been collected and are now available for analysis.

This study is concerned with all cases in which a diagnosis of cancer of the rectum was made in the eleven-year period from 1935 to 1945 inclusive. The patients were admitted to twenty-seven general hospitals, representing approximately 95 per cent of all general-hospital beds in the state. Ward as well as private patients were included, so that no economic level was ignored. The patients were treated by many surgeons in both large and small hospitals. Complete follow-up data were obtained in over 97 per cent of cases. A significant and perhaps unique attempt is therefore made to present a true picture of cancer of the rectum on a state-wide basis.

### Incidence

Cancer of the rectum represented between 4 and 5 per cent of all cases of the disease (Table 1). Although the admission rate of patients with cancer per 100,000 population rose from 131.1 in 1935 to 256.0 in 1945, the percentage of patients with cancer of the rectum rose proportionately to maintain an incidence of 4 or 5 per cent.

In the eleven-year period, 1610 patients were admitted to hospitals with the diagnosis of cancer of the rectum. Of these cases, 1188 were proved microscopically, and in 422 the diagnosis was made

clinically. Only six hospitals had more than 100 cases of cancer of the rectum in the period, and the total number of cases was 983, or 61 per cent of the grand total, twenty-one hospitals had less than 100 cases, representing 39 per cent of the total. Of the microscopically proved cases, 777, or 65.5 per cent, were found in the hospitals with more than 100

TABLE 1 Mortality and Admission Rates for All Cancer and Incidence of Cancer of Rectum

YEAR	AGE ADJUSTED MORTALITY FOR ALL CANCER per 100,000	CRUDE MORTALITY FOR ALL CANCER per 100,000	ADMISSION RATE FOR ALL CANCER per 100,000	ADMISSION RATE FOR CANCER OF RECTUM per 100,000	INCIDENCE OF CANCER OF RECTUM %
1935	111.6	133.3	131.1	6.8	5
1936	107.3	132.5	136.5	5.5	4.0
1937	103	132.3	130.0	6.1	4.1
1938	114.9	145.9	153.4	7.1	4.6
1939	112.3	143.0	179.0	8.0	4.5
1940	118.3	151.1	171.5	8.2	4.8
1941	117.6	154.1	195.0	9.4	4.8
1942	118.0	157.6	203.1	8.2	4.0
1943	118.4	160.9	210.0	10.0	4.8
1944	118.5	169.5	207.0	10.4	5.0
1945	114.2	160.2	256.0	10.4	4.1

cases, and 411 cases, or 34.5 per cent, were discovered in the others.

The incidence of proved cases rose from a low of 58.7 per cent in 1935 to a high of 83.3 per cent in 1942. In this period 73.9 per cent of cases were proved microscopically. In the hospitals with more than 100 cases, 79 per cent of cases were proved microscopically, and in the others only 65.6 per cent were proved (Table 2). Although, in the absence of microscopical evidence of cancer, no scientifically valid conclusions can be drawn, in a high percentage of the unproved cases a diagnosis of cancer of the rectum seemed justifiable. Furthermore, the longevity curve of 220 unproved cases in the first six years coincided almost exactly with that plotted by Daland, Welch and Nathanson<sup>1</sup> for 100 untreated cases of cancer of the rectum, 35 per cent of which were proved microscopically, and with a similar curve plotted for 67 untreated proved cases in this series. For these reasons, wherever it appears to be

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†The tabes and analyses are from the registry of the Division of Cancer and Other Chronic Diseases, Connecticut State Department of Health, Hartford, Connecticut.

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of importance, data on unproved as well as proved cases are presented to obtain a broad comprehension of the present status of cancer of the rectum in the state

### Age

The age distribution in the total proved and unproved cases is presented in Table 3. Slightly over

TABLE 2 *Distribution of Cases according to Microscopical Proof*

YEAR	MICROSCOPICALLY PROVED CASES		CASES NOT PROVED		TOTAL CASES
	NO	PERCENTAGE	NO	PERCENTAGE	
1935	68	58.7	48	41.3	116
1936	66	68.0	31	32.0	97
1937	80	69.0	36	31.0	116
1938	93	75.0	31	25.0	124
1939	100	77.4	42	29.6	142
1940	108	77.2	32	22.8	140
1941	139	80.8	33	19.2	172
1942	119	83.3	24	16.7	143
1943	130	71.5	52	28.5	182
1944	149	78.0	42	22.0	191
1945	136	72.8	51	27.2	187
Totals	1188		422		1610
Averages		73.9		26.1	

60 per cent of patients with proved diagnoses were between fifty and sixty-nine years of age. About 7

TABLE 3 *Age Distribution*

AGE	TOTAL PROVED CASES		TOTAL PROVED AND UNPROVED CASES	
yr	NO	PERCENTAGE	NO	PERCENTAGE
0-9	0	0.0	0	0.0
10-19	1	0.0	2	0.1
20-29	18	1.5	21	1.3
30-39	61	5.2	74	4.6
40-49	146	12.3	171	10.6
50-59	349	29.4	429	26.6
60-69	374	31.5	497	30.8
70-79	201	16.9	333	20.6
80-89	32	2.7	68	4.2
Over 90	0	0.0	4	0.2
Unknown	6	0.5	11	1.0

per cent were below the age of forty, and nearly 20 per cent were above seventy. In the proved cases,

TABLE 4 *Hereditary History of Cancer in Microscopically Proved Cases*

RELATIVE	HEREDITARY HISTORY OF CANCER		HEREDITARY HISTORY OF CANCER AT SAME SITE	
	NO	PERCENTAGE	NO	PERCENTAGE
None	492	41.5	542	45.6
Father	26	2.6	12	1.1
Mother	40	3.4	19	1.6
Brother	15	1.3	7	0.6
More than one brother	2	0.2	2	0.2
Sister	20	1.7	9	0.8
More than one sister	0	0.0	0	0.0
Not specified	573	48.2	564	47.4
Aunts, uncles and others	19	1.6	7	0.6
Unknown	20	1.7	23	1.9

there were 19 patients under thirty. The average age for the total proved and unproved cases was

61.3 years, and for proved cases alone, 63.2 years. The average age for the occurrence of cancer of the rectum is greater than that in other gastrointestinal cancers, and the Connecticut series had a larger

TABLE 5 *Presenting Symptoms*

SYMPTOM	NO OF CASES	PERCENTAGE
Bleeding	812	51.7
Weight loss	602	38.4
Constipation	595	37.9
Frequent stools	438	27.8
Abdominal pains	329	21.0
Local pain	326	20.7
Tenesmus	176	11.2
Hemorrhoids of over six months' duration	132	8.4
Vomiting	128	8.2
Mucus	106	6.8
Polyps	91	5.8
Rumbling of gas	76	4.8
Urinary symptoms	69	4.4
Hemorrhoids of less than six months' duration	46	2.9

proportion of patients in the age groups above seventy than is usually found in the literature.

### Heredity

On the basis of proved cases alone, 4.9 per cent of patients had relatives with cancer at the same site, and in 2.7 per cent of these cases the relative was a parent (Table 4). It should be pointed out that information on heredity was not obtained in 48.2 per cent of cases. If this number of patients is deducted from the total, and rates are based only on cases known to have been questioned, 19.8 per cent had relatives with cancer, and 9 per cent had relatives with cancer of the rectum. The figures are too small to be conclusive, however.

### Signs and Symptoms

The usual presenting symptoms were rectal bleeding, weight loss and some change in bowel habit.

TABLE 6 *Complicating Diseases on Admission*

DISEASE	NO OF CASES	PERCENTAGE
Hypertension or arteriosclerosis	156	10.0
Heart disease	75	4.7
Diabetes	36	2.3
Gastric ulcer	16	1.0
Kidney disease	13	0.8
Pernicious anemia	6	0.4

(Table 5). Local pain and tenesmus were also frequent. The high incidence of weight loss, abdominal pain and vomiting attests to the advanced stage of many cases. Over 11 per cent of patients gave hemorrhoids as the first symptom, and many of these patients had been treated surgically before the cancer was discovered.

In addition, about 20 per cent of patients were found to have some complicating organic disease, notably of cardiovascular origin (Table 6). Diabetes was present in 2.3 per cent, and gastric ulcer in 1.0 per cent of cases. These incidental findings are

probably not unusual in the light of the age groups involved

### Duration of Symptoms

The average delay between the onset of first symptoms and receipt of treatment is presented in Table 7. The median delay in 1935 was 11.2 months.

TABLE 7 Delay between Onset of First Symptoms and Treatment

YEAR	DELAY OF ONE MONTH %	DELAY OF FOUR MONTHS %	DELAY OF SIX MONTHS %	AVERAGE DELAY MO
1935	10.0	31.0	43.6	11.2
1936	7.9	27.8	43.4	8.9
1937	16.4	31.0	51.0	6.9
1938	18.3	45.0	59.1	5.8
1939	17.2	35.8	47.8	7.8
1940	17.0	39.0	53.9	6.6
1941	18.5	39.7	56.0	6.1
1942	21.4	40.0	55.0	6.6
1943	17.6	41.2	54.6	6.5
1944	22.3	46.1	54.8	6.3
1945	20.0	41.0	55.0	6.6

In the subsequent two years, the average dropped to 6.9 months, but no appreciable improvement has occurred in the past eight years. The median delay seems to be fixed between six and seven months. The percentage of patients receiving definitive treatment within one month of the first symptom, however, has doubled in eleven years—from 10 to 20 per cent. The percentage of those receiving treatment within four months has risen from 31 to 41 per cent, and within six months from 44 to 55 per cent.

### Diagnosis

Delay in the recognition of cancer of the rectum should be minimal in view of the striking early symptoms, which focus the attention of both the

TABLE 8 Results of X-ray Diagnosis

NO OF CASES EXAMINED	POSITIVE FINDINGS		NEGATIVE FINDINGS		QUESTIONABLE FINDINGS	
	NO	PER CENTAGE	NO	PER CENTAGE	NO	PER CENTAGE
438	348	79.6	43	9.7	47	10.7

patient and the physician on the lower bowel. Furthermore, in most cases, by the time the first symptoms appear, the disease has already been present sufficiently long to be discovered easily by a careful digital examination. Proctoscopic examination, as well as biopsy, is of value in revealing the few cases that may be difficult to detect with the finger. The value of x-ray diagnosis is indicated somewhat in Table 8.

Only 37 per cent of patients with proved cases had an x-ray examination. In slightly over 20 per cent

the diagnosis was either negative or doubtful. In some Connecticut clinics, radiologists, cognizant of this wide margin of error, now do digital examinations on every patient referred for a barium enema.

### Histologic Grade of Cancers

Connecticut clinics use only three histologic grades. Tissues that might be interpreted as Grade IV according to Broders's<sup>3</sup> classification are included in Grade III. Of the microscopically proved cases 123, or 10.3 per cent, were classified as Grade I, and 582, or 49.0 per cent, as Grade II, thus, nearly 60 per cent of cases were either Grade I or Grade II. Only 110 cases, or 9.3 per cent, were Grade III. In 31.4 per cent the grade was not stated, which

TABLE 9 Resectability according to Year of Admission

YEAR	RESECTIONS	PROVED CASES	RESECTABILITY OF PROVED CASES %	TOTAL CASES	TOTAL RESECTABILITY %
1935-1940	237	515	46.0	735	32.2
1941	66	139	47.5	171	38.4
1942	65	119	54.6	143	45.5
1943	78	130	60.0	182	42.9
1944	93	149	62.4	191	48.7
1945	82	136	60.3	187	43.9
Totals A. cases	621	1188	52.3	1610	38.6

may or may not reflect a trend away from grading in the state.

### Stage of Disease

The extent of the growth in all cases was described as either localized, with involvement of regional lymph nodes or with remote metastases, corresponding in general to Dukes's<sup>2</sup> classification of A, B and C. In the entire period 707 cases (59.5 per cent) were localized, 316 (26.6 per cent) showed regional involvement and 116 (13.9 per cent) had remote metastases on admission. The number of localized cases was 309 (60.0 per cent) between 1935 and 1940 and 398 (59.2 per cent) between 1941 and 1945. The number of patients admitted between 1935 and 1940 with regional involvement—117, or 22.7 per cent—increased over 6 per cent in the last five-year period,—199, or 29.5 per cent,—and this coincided with a drop from 89 (17.3 per cent) to 76 cases (11.3 per cent) with remote metastases in the corresponding periods.

### Resectability

Resectability is determined essentially by the skill and experience of the surgeon, as well as by his attitude toward the choice of radical surgery as a palliative measure in the presence of extensive disease.

In the eleven-year period, the average number of patients admitted annually to the twenty-seven

hospitals was 108. It is apparent that under the present system no one surgeon in the entire state has had an opportunity to do a large series of cases. This must be considered in the evaluation of the

TABLE 10 *Resectability according to Number of Admissions.*

SOURCE OF DATA	TOTAL PROVED AND UNPROVED CASES	TOTAL PROVED CASES	RESECTIONS	RESECTABILITY OF PROVED CASES %	TOTAL RESECTABILITY %
Hospitals with more than 100 admissions for cancer of rectum	983	777	425	54.7	43.2
Hospitals with fewer than 100 admissions for cancer of rectum	627	411	196	47.7	31.3
Totals	1610	1188	621		
Averages				52.3	38.6

resectability rates presented in Table 9. The rate rose from a low of 46 per cent for the years 1935-1940 to a high of 62.4 per cent in 1944. The rate for the entire period was 52.3 per cent. These

TABLE 11 *Procedures in Microscopically Proved Cases*

TREATMENT	NO OF CASES	PERCENTAGE
Resection	621	52.3
One-stage	463	74.6
Two-stage	158	25.4
Colostomy	275	23.1
None	105	8.9
Miscellaneous	76	6.4
Local excision	49	4.1
X-ray and radium	32	2.7
Refused treatment	30	2.5

figures, however, are based on microscopically proved cases only. If all cases are considered, proved and unproved, the rate ranged from 32.2 per cent to 48.7 per cent, and was 38.6 per cent for the

## Treatment

Radical resections were performed in 621, or 52.3 per cent, of microscopically proved cases and in 38.5 per cent of all cases. The procedures in the microscopically proved cases are presented in Table 11. Local excision was performed in 49 cases, usually those with polyps that had undergone malignant change. Only 2.7 per cent were treated by radiation alone, although a number of cases in the miscel-

TABLE 12 *Distribution of Resections*

YEAR	ONE STAGE PROCEDURES	TWO STAGE PROCEDURES	TOTALS
1935-1940	131 (55.3%)	105 (44.7%)	237
1941	48 (72.7%)	18 (27.3%)	66
1942	51 (78.5%)	14 (21.5%)	65
1943	71 (91.0%)	7 (9.0%)	78
1944	87 (93.5%)	6 (6.5%)	93
1945	75 (91.5%)	7 (8.5%)	82
Totals	463 (74.6%)	158 (25.4%)	621

laneous group were treated by radiation combined with some operative procedure.

Of the 275 patients who had colostomies, 41 also had some form of radiation. The operative mortality for colostomies was 28 per cent. A careful study of the records of these cases was made to determine why radical treatment had not been attempted. Some of the patients were candidates for a two-stage resection, but did not survive the colostomy. Other cases were obviously inoperable, and colostomy was attempted as a palliative measure. Approximately 25 per cent of patients seemed to be in good condition on admission, and radical resections might have been attempted in bolder and more skillful hands.

Of the 105 patients for whom no treatment was recommended, 45 per cent were over seventy years

TABLE 13 *Age Distribution according to Treatment (Microscopically Proved Cases)*

TREATMENT	AVERAGE AGE	PATIENTS UNDER 40 %	PATIENTS 40-59 %	PATIENTS 60-69 %	PATIENTS 70 AND OVER %	AGE NOT SPECIFIED %
Resection	57.7	7.0	47.8	33.1	11.9	0.2
Colostomy	61.1	6.2	39.4	26.9	25.9	1.6
Local excision	61.7	8.2	32.6	28.6	30.6	0.0
None	64.9	1.0	27.6	37.1	33.3	1.0
X-ray and radium	65.0	0.0	25.0	43.7	31.3	0.0
Refused treatment	68.0	0.0	26.6	26.8	46.6	0.0
Miscellaneous	56.3	18.4	38.2	25.0	18.4	0.0
Averages	63.2	6.7	41.7	31.5	19.6	0.5

entire period. None of the patients with unproved cases had resections, but a different significance is attached to the rates when they are based on total cases rather than on microscopically proved cases alone.

The resectability rate in hospitals with more than 100 cases was 7 per cent higher for proved cases, and 12 per cent higher for total cases, than that in hospitals with less than 100 cases (Table 10).

of age, about 50 per cent were considered to be in poor general condition, and over 21 per cent had remote metastases on admission. The average duration of life from the first symptom to death for this group was 21.3 months.

The unproved cases were treated as follows: colostomy, 214 cases; no treatment, 187 cases; radiation, 15 cases; and miscellaneous, 6 cases. No unproved case was submitted to radical resection.

Of the 621 resections, 74.6 per cent were one-stage abdominoperineal operations, and 25.4 per cent were performed in two stages, either by the Lahev<sup>2</sup>

in 384 cases, with a mortality of 18.4 per cent. Similarly, in the period of 1935-1940 one-stage resections were done in 131 cases, with a mortality of

TABLE 14 Operative Mortality following Radical Resection

YEAR	ONE-STAGE RESECTIONS	OPERATIVE DEATHS	TWO-STAGE RESECTIONS	OPERATIVE DEATHS	ALL RESECTIONS	OPERATIVE DEATHS
1935-1940	131	33 (25.2%)	106	26 (24.5%)	237	59 (24.9%)
1941	48	8 (16.7%)	18	5 (27.8%)	66	13 (19.7%)
1942	51	5 (9.8%)	14	3 (21.4%)	65	8 (12.3%)
1943	71	16 (22.5%)	7	1 (14.3%)	78	17 (21.8%)
1944	87	15 (17.3%)	6	3 (50.0%)	93	18 (19.4%)
1945	75	11 (14.7%)	7	4 (57.2%)	82	15 (18.3%)
Totals	464	88 (19.0%)	158	42 (26.6%)	621	130 (20.9%)

method or by colostomy followed by perineal resection (Table 12).

There was a striking increase in the frequency of one-stage resections during the eleven-year period. Between 1935 and 1940 one-stage operations represented 55.3 per cent of total resections, and 44.7 per cent were done in two stages. In the past three years,

25.2 per cent. In the last five years, one-stage resections were performed in 332 cases, with a mortality of 16.5 per cent. In 1945 the mortality for one-stage resections had dropped to 14.7 per cent.

TABLE 16 Factors Influencing the Five Year-Cure Rate in 515 Cases

FACTOR	TOTAL NO OF CASES	FIVE YEAR CURE	
		NO	PERCENTAGE
Age in years:			
Below 40	69	9	13.0
41-50	26	10	38.5
51-60	104	19	17.7
61-70	127	14	11.0
Over 70	185	6	3.2
Sex:			
Males	298	30	10.0
Females	77	28	12.3
Stage of disease:			
Localized	509	49	15.8
Regional involvement	11	9	7.7
Remote metastases	89	0	0.0
Metastases:			
None	291	49	16.9
Present on admission	187	9	4.8
Developed after admission	37	0	0.0
Histopathologic grade of tumor:			
I	51	11	20.8
II	20	26	11.8
III	54	3	5.6
Not stated	188	18	9.6

TABLE 15 Causes of Postoperative Deaths

CAUSE	NO OF CASES	PERCENTAGE
Peritonitis	23	17
Surgical shock	22	16.9
Cardiovascular failure	21	16.2
Pulmonary embolism	11	8.4
Pulmonary complications	10	7.9
Urinary complications	8	6.2
Paralytic ileus	10	7.7
Miscellaneous	18	13.8
Not stated	—	—
Total	130	—

over 90 per cent of resections were performed in one stage.

Of all resections, 45 per cent were done on patients over sixty years of age. The age distribution for all forms of treatment is presented in Table 13.

### Operative Mortality

The rising resectability rate has been accompanied by a lowering of operative mortality (Table 14). In

The mortality for two-stage resections was 24.5 per cent between 1935 and 1940, and 26.6 per cent for the entire period. Since the number of one-stage

TABLE 17 Five Year End Results

RESULT	ALL MICROSCOPICALLY PROVED CASES	CASES WITH RESECTION
Unknown:	12	8
Death from other cause without recurrence	10	7
Patient lost to follow up probably without recurrence	2	1
Failure:	445	192
Death from cancer	420	180
Patient lost to follow up (probably dead)	13	4
Survival with recurrence	12	8
Cure (patient free from disease)	58 (11.5%)	37 (16.1%)
Totals	515	237

\*Percentage of known results

the period 1935-1940 resections were performed in 237 cases, with an operative mortality of 24.9 per cent. Between 1941 and 1945 resections were done

resections increased, two-stage operations were obviously reserved for the patients regarded as poor risks.

### Causes of Death

The causes of postoperative death are presented in Table 15. The most frequent ones were peritonitis and shock. The next most important was

in the six-year period 1935-1940 (Table 16). Above the age of forty years there appears to be a steady drop in five-year-cure rates as the age increases. Little difference is manifested between the sexes

TABLE 18 *Survival and Cure Rates on the Basis of Complete and Selected Totals in General Use*

BASIS OF ESTIMATE	TOTAL CASES	FIVE YEAR SURVIVALS		FIVE-YEAR CURES	
		NO.	PERCENTAGE	NO.	PERCENTAGE
Total admissions	735	94	12.8	58	7.9
Total proved cases	515	85	16.5	58	11.2
Proved cases with known results	503	85	16.9	58	11.5
Total resections	237	60	25.3	37	15.6
All resections except cases with remote metastases	214	57	26.6	37	17.3
All survivals	178	57	32.0	37	20.8
Survivals without remote metastases	161	57	35.4	37	23.0

cardiovascular failure, including cerebral hemorrhage, myocardial failure, mesenteric thrombosis and ruptured aneurysm. Pulmonary embolism accounted for 8.4 per cent of deaths, and pneu-

Localized growths and a low histologic grading appear to be favorable factors.

### Results

In reviewing the literature on cancer of the rectum in the past ten years, one is impressed with the lack of uniformity in reporting end results. This makes for ambiguity of interpretation and difficulty of comparison. In this series the method of computing five-year cures suggested by Martin<sup>4</sup> was employed. Strict and logical criteria are established for determination of cure, and accurate follow-up study in over 90 per cent of cases is necessary. On this basis, five-year cures were obtained in 11.5 per cent of the 515 proved cases with known results observed during 1935-1940, and in 16.1 per cent of the resected cases (Table 17).

This estimation of cures, however, does not take into account the relatively large number of unproved cases. With the view of advocating the adoption of a standard method of reporting end results, the estimate was revised (Table 18). The variety of results that may be claimed, depending on the basis used for calculation, is apparent.

Beginning with a five-year-cure rate of 7.9 per cent based on all cases and a five-year survival rate of 12.8 per cent, there is a progressive rise to an optimistic figure of 35 per cent as different denominators are used. Statistics thus computed show the possibilities of accomplishment in selected cases, but tend to obscure the total picture.

Comparative longevity curves in resected cases, cases in which colostomies were performed, cases in which no treatment was given and unproved cases are presented in Figure 1.

\* \* \*

Although a detailed and critical analysis of the findings is not possible in this presentation, sufficient information has been submitted to indicate the value of collecting cancer statistics on a state-wide basis.

A continued effort must be made to reduce the time lag between the first symptom and definitive

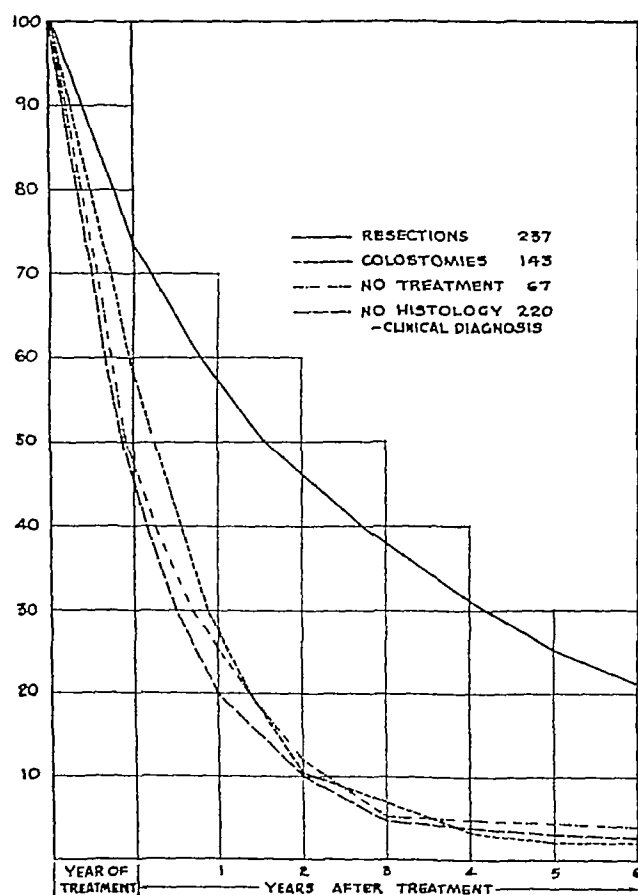


FIGURE 1 *Percentages of Survivals after Hospitalization for Cancer of the Rectum (based on the 1935-1940 records of twenty-seven general hospitals)*

monia and atelectasis for 7.9 per cent. Urinary complications caused 6.2 per cent of deaths.

### Factors Influencing Cure

Data on factors that have been considered to influence curability are based on cases admitted

treatment. The signs and symptoms of cancer of the rectum are sufficiently striking to warrant early recognition by both the patient and the physician.

Biopsy should be performed in all cases if an accurate appraisal is to be made.

Operability and mortality rates are improving, owing perhaps to the use of antibiotics in the prevention and treatment of sepsis, a better understanding of the management of shock and phlebitis and the more widespread employment of trained physician-anesthetists. Further improvement might be possible if some plan could be adopted of concentrating the care of these cases in a few centers.

For the six-year period 1935-1940, five-year cures were obtained in only 7.9 per cent of all cases. In the microscopically proved cases 11.5 per cent of patients were cured at the end of five years. More favorable results can be shown in selected cases, as reported in the literature. This suggests that a uniform method of reporting end results is highly desirable in the interest of a precise evaluation of the status of cancer of any organ.

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#### DISCUSSION

DR. ASHLEY W. OUGHTERSON (New York City): Ten years ago the Connecticut Tumor Society inaugurated this program, and this paper that we have had the privilege of hearing today is the first summary of 1610 cases of cancer of the rectum out of a total of more than 35,000 cancer cases.

Connecticut doctors should be congratulated since this represents some of the best of medicine as a social science, and there has been a great trend in recent years toward considering medicine a social science.

The general practitioner, the specialist, the State Department of Health and the hospitals have joined in a co-operative effort to discover what happens in one of man's most insidious and dangerous diseases.

The paper just presented is important because, to my knowledge, it represents the first time in America that a cross section of the population has been studied as treated and diagnosed by a cross section of the physicians. Such a study, and the remainder of these facts in Connecticut as they are brought out, should provide us with the sinews for the war against cancer to point the way to what is needed and to indicate the effectiveness of cancer control.

These results are obviously not so favorable as they could have been, but they are not so poor as they might have been. Much has been heard of the results in the large hospitals and clinics which have performed a great service in showing what can be done, but by this time we know that their results are good and we need to hear more of the other side of the story.

Medicine as a social science cannot be judged solely by the results in the large hospitals and clinics. One must go to the average hospital inhabited by the average patient, who is treated by the average physician to evaluate the position of medicine as a social science.

This material is extraordinarily valuable at the present moment because of the attack on cancer in which many of us are engaged in inaugurating and guiding. The large sums of money that are becoming available raise a pertinent question — how this money should be spent. It has been stated that 30 to 50 per cent of patients with cancer can be saved by the proper or adequate use of the methods that are available. I doubt whether that figure is accurate because to my knowledge the facts have not been obtained from a cross section of the population.

Here, for the first time, is a co-operative effort within a state to furnish that information so that by proper analysis it can be stated with reasonable accuracy after this study is completed what can be accomplished by education in the use of the methods that are available. Then it can be determined how much of the national resources of money, men and materials should be spent on the use of the weapons at hand while research for the future is being conducted.

No one knows when the cause of cancer or a new means of cure will be discovered. Many authorities actually doubt whether there will be a universal cure. It is therefore imperative at present, when promises of what will be done to cure cancer are being made, to obtain concrete results.



## INFECTIOUS HEPATITIS WITH SUBACUTE ATROPHY OF THE LIVER\*

## An Epidemic in Women after the Menopause

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**A**N unusual and serious epidemic of infectious hepatitis has been present in Denmark since 1944. It differs from epidemics previously described in that the course has been extremely malignant and the disease, which is usually fatal, occurs almost exclusively in women after the menopause.

In 1945 attention was called to this form of hepatitis in Denmark,<sup>1</sup> and several other observers have had similar experiences.<sup>2-4</sup> Since in most patients the disease progresses in a characteristic and uniform manner, the symptoms by which it has generally been manifested in our department are described below.

As a rule the patient is an elderly or middle-aged woman. For a month or two she has suffered from lassitude, epigastric oppression, loss of appetite turning to an aversion to food and nausea. Occasionally, vomiting occurs. The patient is hospitalized for gradually increasing jaundice, which begins after the initial stage described above. At times the first symptom is a brief febrile period or perhaps diarrhea. During the subsequent course, however, the temperature is seldom high, the icterus varies in intensity but is often only moderate. It may last until exitus, but this is not the rule. The jaundice often has a tendency to recede while the patient is confined to bed, although this does not justify a more favorable prognosis. Since icterus may vary greatly within a relatively short time and there often are colicky pains in the right upper quadrant, it is not surprising that the differential diagnosis from cholelithiasis is difficult.

In the icteric stage the patient's appetite usually decreases. She complains of a bad taste in the mouth. The lassitude grows, and she may spend the whole day drowsing. Five or six months after the onset the patient is usually troubled by increasing ascites and edema. She may lie for months in this condition. With parched mucosa, ecchymosis, decubitus ulcers, massive ascites and edema, the patient is a wretched sight before passing at last into the phase of hepatic coma — an event that usually happens ten or twelve months after the appearance of the first vague symptoms.

The post-mortem findings are just as characteristic as those of the clinical picture. Usually, the liver is extremely atrophic, weighing only 600 to 800 gm. Even macroscopically the lesion seems distinguishable from the ordinary portal cirrhosis. The surface

is lighter in color than normal. In some areas there are small islands of preserved liver tissue, differing from the surrounding areas by their yellowish color and projecting somewhat from the general surface, which shows many retractions due to areas of atrophy where the liver cells are replaced by connective tissue. The cut surface shows similar features. Here, too, the predominant feature is the homogeneous connective-tissue stroma, with scanty areas of preserved liver tissue.

On microscopical examination the central part of the acinus is seen to be the site of degenerative changes, with incipient inflammatory infiltration. The central vein and capillaries are dilated, and the liver cells atrophic and necrotic. There is proliferation of the Kupffer cells and infiltration with leukocytes, lymphocytes and phagocytic cells. In the periphery of the acinus the liver cells are preserved fairly well, being arranged in columns or trabeculae. This is the picture encountered at a relatively early stage. When the process is more advanced, the greater part of the original liver parenchyma has disappeared, leaving merely scattered small islands of liver cells; the rest of the organ is made up of connective tissue rich in cells, with isolated groups of vessels.

The changes correspond exactly to the picture of subacute yellow atrophy of the liver described by Bergstrand<sup>5</sup> in 1930, or to that in protracted cases of liver atrophy described by Lucké<sup>6</sup> in 1944. Microscopically, the lesion differs distinctly from portal cirrhosis, in which the changes seem to have begun in the periphery of the lobule.

Even at an early stage liver-function tests indicate a grave parenchymatous lesion. The Takata reaction, which must be emphasized as a reliable test, is strongly positive in nearly all cases of chronic hepatitis. The icteric index is moderately high as a rule, fluctuates to some extent during the course of the disease and in the terminal stage may show normal values. The urobilinogen in the urine is generally increased. The thymol reaction is usually markedly positive, and the sedimentation rate increased, as is the relative globulin content of the serum.

The following is an account of the epidemic of chronic hepatitis observed since 1944 at Bispebjerg Hospital, Department B, chiefly among elderly and middle-aged women. For comparison I have collected all cases of infectious hepatitis recorded in the Department from 1928 to 1945, a total of 550 cases. Of these, 396 followed an acute course, — that is, the duration was under three months, — and

\*From Bispebjerg Hospital (chief, Dr E. Meulengracht). This study was supported by a grant from the P. Carl Petersen Foundation.

†Senior assistant in medicine, Bispebjerg Hospital.

154 were chronic—of more than three months' duration

Figure 1 shows that the number of chronic cases increased rapidly in 1944 and 1945, the total in these

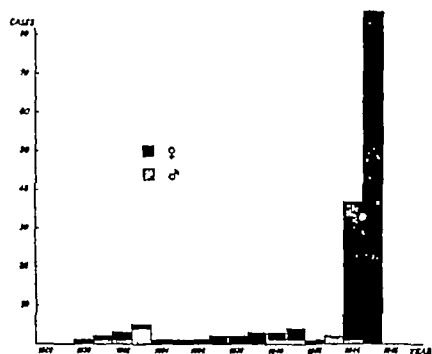


FIGURE 1 Infectious Hepatitis of More Than Three Months' Duration at Bispebjerg Hospital (Department B) during 1928-1945

two years being 123, whereas in the foregoing sixteen years there had been only 31 cases. It also appears that during the epidemic the chronic cases oc-

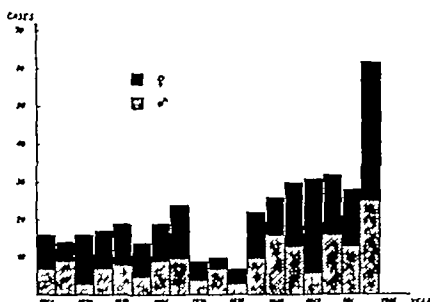


FIGURE 2 Infectious Hepatitis of Less Than Three Months' Duration at Bispebjerg Hospital (Department B) during 1928-1945

curred almost exclusively among women (1 male and 122 female patients)

Figure 2 presents the distribution of the 396 acute cases. The incidence was about equally distributed between the sexes, despite the fact that the women's department is larger than the men's.

Figure 3 comprises all cases of infectious hepatitis reported to the authorities from all over the coun-

try. It will be observed that there were two epidemics, the maximum number of cases occurring in one in 1933 and in the other in 1943, in the latter year there were 18,000 cases of infectious hepatitis (six times more than the normal) throughout the country, whose total population is 4,000,000.

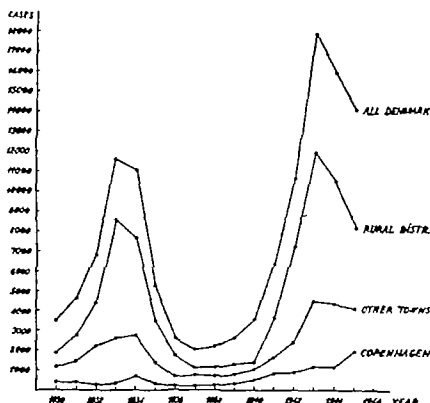


FIGURE 3 Infectious Hepatitis in All Denmark and Various Districts during 1930-1945

Figure 4 presents the fatal cases of infectious hepatitis, including acute and chronic atrophy of the liver. During the 1944-1945 epidemic 75 patients died, only 1 of them being a man, thus, nearly 99 per cent of the fatal cases occurred in women. Of all hospitalized patients with infectious hepatitis in these two years 35 per cent died, and in all cases with a duration of over three months the mortality

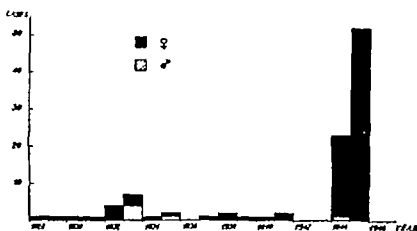


FIGURE 4 Fatal Cases of Infectious Hepatitis according to Sex, at Bispebjerg Hospital (Department B)

was 67 per cent. It is probable that this extremely high mortality will increase when the period of observation is lengthened.

Chronic hepatitis occurs chiefly in patients above fifty years of age (Table 1), 71 per cent of patients were over fifty, and 90 per cent over forty years, whereas the acute form usually affected people chiefly between the ages of fifteen and thirty. Eighty-

TABLE 1 *Age Distribution in Infectious Hepatitis*

AGE yr	CHRONIC CASES*	ACUTE CASES†	FATAL CASES
0-14	2	43	0
15-30	6	188	—
31-40	6	76	3
41-50	30	41	8
Over 50	110	48	64
Totals	154	396	75

\*More than three months' duration

†Less than three months' duration

five per cent of the patients who died in 1944-1945 were over fifty years of age.

A characteristic feature of chronic hepatitis is the long preicteric phase in which the patients complain of tiredness, loss of appetite and weight. Table 2 shows that during the 1944-1945 epidemic the preicteric phase lasted more than a month in 64 per cent of the chronic cases, and in 32 per cent the duration was over two months. In 100 successive cases of acute hepatitis the preicteric phase lasted less than fourteen days in 92 per cent.

Ascites and edema are frequent complications in chronic hepatitis. These symptoms generally occur simultaneously. Of 123 patients 66 per cent had edema and ascites, in most cases about six months after the first manifestation of the symptoms, 6 of the patients never had jaundice. The duration of the chronic hepatitis, determined from the appear-

TABLE 2 *Duration of Preicteric Phase*

DURATION wk	CHRONIC CASES	ACUTE CASES
Less than 1	15 (14%)	60 (60%)
1-2	8 (7%)	32 (32%)
2-3	10 (9%)	5 (5%)
3-4	7 (6%)	2 (2%)
4-8	35 (32%)	1 (1%)
Over 8	36 (32%)	0
Totals	111	100

ance of the initial symptoms, in 75 fatal cases is presented in Table 3. The average duration was nine months.

The fulminant occurrence of malignant, protracted hepatitis in women after the menopause seems to be unique and has not previously been described in epidemics in or outside Denmark.

During an epidemic in Sweden in 1928 Bergstrand<sup>5</sup> found that 72 per cent of the malignant cases of hepatitis occurred in women. There, however, the affection was apparently acute atrophy of the liver,

terminating fatally in the course of from four to six weeks. Of Bergstrand's patients 37 per cent were women over forty-five years of age.

Lucké<sup>6</sup> describes 125 fatal cases during an epidemic of hepatitis among soldiers in 1942. Here again, acute atrophy of the liver led to death in four to six weeks. In both Bergstrand's and Lucké's material the preicteric initial phase did not last more than two weeks as a rule, as in the acute cases described above.

The natural assumption is that this is a disease previously unknown in Denmark and differing markedly from the ordinary form of infectious hepatitis. The chronic hepatitis in the 1944-1945 epidemic occurred chiefly among elderly women, whereas acute hepatitis attacked younger people with no particular regard to sex.

The chronic form often has a preicteric phase of several months' duration, with gradually increasing tiredness and nausea, whereas acute hepatitis gener-

TABLE 3 *Duration of Hepatitis in 75 Fatal Cases 1944-1945*

DURATION mo	NO OF CASES	PERCENTAGE
1-3	7	9
4-6	18	24
7-9	17	23
10-12	14	19
13-15	8	11
16-18	7	9
19-21	3	4
Over 21	1	1

ally has a preicteric phase of no more than a week, so that at the beginning of the jaundice one can often predict the course of the disease.

In chronic hepatitis the icterus often varies considerably in degree, sometimes, it subsides completely, even if the disease progresses. This is rarely true of the acute form.

Of the patients with chronic hepatitis 4 had previously had infectious hepatitis and had been well in the meantime. This suggests that the first attack left no immunity to the next one. Acute hepatitis rarely occurs more than once in the same patient if relapses are disregarded.

It seems possible for chronic hepatitis to be transmitted by contact, and for the person so infected the course is equally grave. In 4 cases of chronic hepatitis the lesion possibly arose through contact with other patients. These 4 patients were elderly women who for some time had nursed their respective female relatives who had been suffering from chronic hepatitis. The disease had an incubation period of up to two months in the 4 cases and followed a fatal course in the contacts as well as in the original patients.

There are certain points of resemblance between serum hepatitis and this chronic form. According to Findlay et al.,<sup>7</sup> Havens<sup>8</sup> and Neefe, Stokes and

Gellis,<sup>8</sup> serum hepatitis has a long incubation period and sometimes a graver course than infectious hepatitis. It has never been demonstrated that serum hepatitis can infect by contact, nor in fact has such transmission been proved in chronic hepatitis. Since the infectious substance of serum hepatitis can be transmitted on the point of a knife that has been wiped after blood sampling from the ear, there does not seem to be anything improbable in transmission via an insect bite. Among the nurses in the department there has been no case of chronic hepatitis, although no special measures were taken to avoid infection.

I should not neglect to raise the question of whether these elderly women had suffered under dietary insufficiency, especially a protein deficiency. Since they were by no means particularly poor or underfed, this possibility may be ignored, especially because none of them presented signs of dietary insufficiency, indeed, no such symptoms were observed in Denmark during the war.

A feature common to almost all women with chronic hepatitis is that they had passed the menopause. In several of the younger patients with chronic hepatitis the menses failed while the affection lasted, sometimes for more than a year. On this basis it is tempting to assume that in some way the female sex hormone has a bearing on the course of the infection. The fact seems established that the estrogens are neutralized in the liver,<sup>10-12</sup> and certain hormonally conditioned changes have been observed in patients with liver lesions, such as gynecomastia and atrophy of the testes in males with cirrhosis of the liver.<sup>13</sup>

So far as the excretion of estrogens in this form of hepatic lesion is concerned, nothing has been done beyond certain initial investigations. Nevertheless, it is a problem that may become of practical importance, if it should turn out that in women the estrogens exert some form of liver-protecting influence against the infection.

## SUMMARY

An account of an epidemic of chronic hepatitis in Copenhagen in 1944-1945 is presented. In a single department of a hospital 123 patients were treated for the disease, which is characterized by a protracted course (over three months) and by the occurrence of ascites and edema. Over 99 per cent of cases occurred in women. The mortality was high — 61 per cent. The disease chiefly affected women after the menopause, 79 per cent of patients during the epidemic being over fifty years of age, and is often characterized by a long preicteric phase — more than four weeks in 64 per cent — in contrast to acute infectious hepatitis, in which the preicteric phase in 92 per cent of patients was less than two weeks. The average duration of the disease in the fatal cases was nine months.

The possibility of a special malignant virus is emphasized, and the question is raised whether estrogens exert some form of liver-protecting influence against this particular infection.

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## BOSTON MEDICAL LIBRARY

## Report of the President\*

IT IS an annual custom for the President to inform the fellows of the condition of the Library. It is my pleasant duty to present my first annual report

The status of medical libraries in Boston has been a subject of discussion for some years. In 1941 a survey of this situation was made by Mr. Thomas P. Fleming, medical librarian of Columbia University, and his comprehensive report was studied by a committee consisting of Mr. Fleming and Drs. John F. Fulton and Robert N. Nye. This committee brought out the following points:

In general, medical institutions in Boston have excellent resources of medical literature within relatively easy access.

The physical facilities of the working libraries in the medical schools are in need of considerable readjustment.

The administration of all working libraries has not attained general standards of medical libraries in other parts of the country.

The Boston Medical Library is centrally located and has sufficient storage space for many years to come, particularly in view of the facilities offered by the New England Deposit Library.

The Boston Medical Library, because of lack of funds, is understaffed and does not furnish the type of service, regarding either quantity or quality, that is to be expected.

The future of the Boston Medical Library, particularly in view of present-day attempts to eliminate decentralization and duplication, hinges about its development as a *reference library*, for the benefit not only of Boston and its immediate vicinity but also of the rest of Massachusetts and the other New England states.

The committee recommended that steps be taken to actuate these observations.

The trustees have endeavored to find ways and means of accomplishing at least some of these suggestions. The results have been discouraging. Dr. Cheever, in his last annual report, described in detail the various attempts to get more income. A drive for more fellows has brought in perhaps \$2500 more, the professional members at \$50 each have increased somewhat and the Suffolk District Medical Society and several special societies have been most generous. In spite of this, our income has averaged only about \$30,000 a year, and without expanding at all we run behind about \$1000 a year. That the Library has been able to offer any reasonable service has been due to the untiring

efforts of our librarian, Dr. Viets, and of our director, Mr. Ballard, and his small but devoted staff.

A library of over 200,000 volumes and almost as many pamphlets, to say nothing of its almost priceless collection of incunabula, Hebraica, early medical-history and biographic collections, which are of national importance, certainly deserves better and more widespread support.

The Massachusetts Medical Society and the Boston Medical Library have grown up hand in hand. The founders of the Library were all members of the Society. Although the Massachusetts Medical Society gave its books to the Boston Public Library in 1872, it was apparently satisfied to turn to the Boston Medical Library as a place for its meetings and its general headquarters, and in February, 1879, it was voted "That the treasurer of the Society be authorized to conclude arrangements with the Boston Medical Library Association by which councilors of the Massachusetts Medical Society, together with its standing committees, may hold their meetings at the rooms of the Library Association during a term of ten years." The Library has continued to be the headquarters of the Society ever since. In June, 1885, a recommendation of the Committee on Library, through Dr. Z. B. Adams, stated that the library of the Massachusetts Medical Society consisted mainly of reports of various medical societies, and it was voted "That that property and all similar publications hereafter received be given to the Boston Medical Library on condition that they be accessible to members of the Society."

The Massachusetts Medical Society assumed ownership of the *New England Journal of Medicine* in 1921, and during the years that the *Journal* staff has occupied offices in the Library building, there has been a close and cordial association. The editor is treasurer of the Library, and the *Journal* deposits its books received for review with the Library.

The intimate association of these two societies appears to have been mutually beneficial during the years, and there seems to be no reason to believe that they should not continue so for many years to come. Indeed, there have been several attempts to a closer relation and even a suggestion of an actual merger of the two societies under the name of an academy of medicine. When these possibilities were more carefully explored it was found that the legal obstacles in the way were insurmountable, largely because of the many trust funds held by the Library for special purposes.

A well equipped and well staffed reference library is an essential branch of medicine both for the

\*Presented at the annual meeting of the Boston Medical Library, March 4, 1947.

practicing physician and for the research worker. The Library offers its service to all members of the medical profession in Massachusetts, whether or not they are fellows. It occupies the same relation to the physicians of the Commonwealth that a free public library does to the citizens of its community. The citizens support a public library by means of taxes willingly enough, although many of them never use it. They recognize that it is a necessary adjunct to society as a whole. So should the medical profession consider the Boston Medical Library an adjunct to the profession of medicine in Massachusetts and be glad and willing to support it.

It seems logical then that the Massachusetts Medical Society, which represents over five thousand and out of perhaps eight thousand physicians in Massachusetts, should be glad and willing to assume some of the financial responsibility of the Library and thus allow it to put its house in order, enlarge its personnel and offer the reference-library service for which it is otherwise well equipped.

It is a pleasure to report that this has been accomplished. When the Executive Committee of the Council and the Council itself were presented with the facts, they were convinced that the Library could not function as a great library should without the help of the Society. It was therefore voted that \$5 00 out of the increased annual dues be allocated to the Boston Medical Library, with the sole proviso that it be legal and that every member of the Society be made a member of the Library in some category.

Our counsel, who is also counsel for the Massachusetts Medical Society, has rendered an opinion that the Massachusetts Medical Society may lawfully contribute toward the support of the Library. The matter of membership requires some change in the by-laws, and the trustees have authorized me to appoint a special committee to consider this matter. It will be necessary for the fellows to act on any report that may be rendered, and you may expect to be called in special meeting at some time in the near future.

This generous response of the Massachusetts Medical Society will give us next year an added income of over \$25,000. We may lose some fellows, particularly in the nonresident category, but it is hoped that loyalty to the institution and a sense of ownership in the Library will persuade most to retain their fellowships.

So far as plans for the future are concerned, we are fortunate in having the wise and sympathetic counsel of Mr. Keyes D. Metcalf, Director of Libraries of Harvard University. He is intensely interested in our problem, has made a survey of our needs and has offered certain recommendations. I shall leave the discussion of these, for the most part, to our librarian, Dr. Viets. I should like to make a few comments, however.

Mr. Metcalf's first suggestion is to make the Library a first-rate reference collection and, to accomplish this, to weed out unwanted medical and nonmedical books and periodicals and deposit them in the New England Deposit Library. At their last meeting the trustees voted to take this first step without delay. They authorized the Librarian to take space in the New England Deposit Library and to carry out the weeding process little by little during the summer. Books placed in this deposit library will always be available on reasonable notice. This will give us room enough to sort out volumes accumulated in odd places and to place them properly on shelves.

Another necessary undertaking is the completion of the union catalogue of the holdings of all the medical libraries in the Boston area, so that the Boston Medical Library can take its place as the central institution among them. The basis for this catalogue already exists on cards, but the system is far from complete.

We must in the near future give some consideration to the establishment of a pension system for our employees, who, it must be remembered, are not eligible for Social Security benefits.

I hope that we shall be able to put away a little money each year toward the completion of the stacks in the stack building and the elevator to serve them. Five floors of stacks are yet to be completed. Perhaps after we complete our new organization and put our house in order, a special drive for funds should be made for this purpose.

Although there are probably many obstacles in the way of complete realization of our ideals, we are at least embarked on the voyage. I am sure that with the loyal help and support of the fellows, the trustees will give their time and thought to the various problems as they arise to enable us to furnish the type of library service that the Boston Medical Library is well equipped to offer.

WALTER G. PHIPPEN

## Report of the Librarian\*

IT IS again the privilege of the Librarian to present to the Corporation of the Boston Medical Library his annual report—in this instance, his ninth accounting of the state of the Library. You, as fellows of the Library and owners of the building and its contents, will wish to know whether adequate service has been rendered to our readers, how well the collection has been maintained and what plans are contemplated to carry forward the fundamental aims of the Library in the next few years. The goal in general is the ever-elusive one of complete usefulness to its users, both private and public, of the entire contents of its collections, continually enriched by the addition of treasures from the past and a judicious selection of the medical literature of the present.

### SERVICE TO READERS

Both the use of the Library and the attendance increased greatly in 1946 over 1945. The circulation of books reached a total of over 38,000—an increase of more than 20 per cent. This is nearly the average of the prewar years, for in 1940 and 1941 about 40,000 items were taken off the shelves for our readers each year. During World War II the number fell to about half, indicating how much the Library is used by the younger members of the profession. The same trend is shown by the attendance figures. In 1946 over 10,000 visits were made to the Library. The figure, an increase of 46 per cent over 1945, is about the average for the prewar years.

We thus resumed in 1946 our usual activity both in the number of readers and the number of items that they used. The collection was made available in a satisfactory manner in spite of some delays due to the shortage of personnel. The interlibrary loans more than doubled in 1946, showing that the Library is being used frequently for purposes of research by other institutions. We are thus rendering an excellent service in furnishing material to the Harvard University libraries, the libraries of the Boston hospitals and other institutions nearby, as well as those at a distance. The Library was used by the Newton-Wellesley Hospital, the Rhode Island Medical Society in Providence, Smith College in Northampton, the United Shoe Machinery Company in Beverly, the Winchester Public Library and many others. Our largest interlibrary loan service at present, as it should be, is to the Veterans Bureau hospitals. We have sent books, however, all the way from Bar Harbor, Maine, to Dallas, Texas, and San Francisco, California, and even some interested reader from Myrtle Beach, South Carolina, sought a book that presumably could not be found elsewhere. In the course of the year, our members

used the Library over twenty-five hundred times and on the average took out ten books or journals apiece. The fellows used about 60 per cent of their books in Holmes Hall, and 40 per cent were taken home. There were three times as many visitors as there were fellows, but they used only half as many items. This proportion seems proper and indicates that we are serving our fellows well and, in addition, taking care of the needs of our visitors, mostly students. On the two evenings a week that the Library is open we draw only a small percentage of our total members but a much larger number of visitors.

### GROWTH AND MAINTENANCE OF THE LIBRARY

As predicted a year ago, the Library contains over 200,000 volumes, and the pamphlets number 140,000, a collection of 340,000 medical items being thus available to the medical profession in Boston and its vicinity, as well as to scholars throughout the country. The Library added about the usual number of books and periodicals in 1946. A large group of French theses were deposited by the Harvard Medical School Library. As might have been expected after the war years, the number of periodicals taken currently by the Library increased from 578 in 1945 to 723 in 1946. Most of the increase was in foreign-language periodicals, a gain from 44 to 139. We are not up to the record number of journals received in 1937,—namely, 907,—but this is largely accounted for by the fact that only 2 German periodicals were received in 1946. The foreign journals of the war years, 1940–1945, however, are beginning to come in. Early in 1947, the German periodicals for the years 1940 and 1941 were received and many of the Dutch, Scandinavian, Swiss, French and Italian journals from 1940 to 1945 have also been placed on our shelves. Our book dealers in Europe, old and loyal friends of the Library, kept files so far as possible of all medical periodicals, and it was a pleasure again to open packages of large contributions from Nijhoff in The Hague, Le François in Paris, Nardecchia in Rome, Enslin in Berlin and Haus der Bucher in Geneva. An active foreign exchange was continued with the Soviet Union, and about 27 of the current Russian medical periodicals were received, some of these sets are nearing completion. In exchange we are sending standard American medical periodicals to Russia, and later we hope to expand into books and pamphlets. We are also receiving Russian journals from the Harvard Medical School Library, and plans are being worked out to centralize all Russian medical literature in Boston in the Boston Medical Library.

The Library is still falling behind in the binding of its periodicals, only 378 volumes of the 723 periodicals received being bound in 1946. We thus

\*Presented in part at the annual meeting of the Boston Medical Library, March 4, 1947.

added to our accumulation of volumes needing binding. The division of current literature, most used by the fellows, should be kept up to a high degree of standard by an increase in the number of periodicals and by the binding of those that are extensively used.

### THE FUTURE

The available stacks are overloaded with books and periodicals, volumes and loose numbers of journals and pamphlets have to rest on the floor. To provide for future accessions, we should build the new addition to our stacks immediately or seek room elsewhere for the storage of little-used material. Possibly, the character of accessions should be changed so that fewer books and journals come into the Library each year. Of the solutions proposed to meet our needs, the new stacks seem to the Librarian the most important, and he again calls the attention of the fellows to the great need for building the remaining tiers of the stacks, already so useful in their abbreviated form. The building is ready to house them, and we can probably arrange to get the steel to complete the seven additional tiers.

Another method of lesser value is being employed for immediate relief. Arrangements have recently been made to take over a section of the New England Deposit Library in Cambridge, and this will become available to us on July 1. The New England Deposit Library was established about six years ago under the auspices of Harvard University, and a building erected on Western Avenue in Brighton in the rear of the Harvard Business School. Space in this building is now rented by the Boston Public Library, the Boston Athenaeum, the Massachusetts State Library and other neighbor libraries. More than half the space is used by the Harvard College Library. At present the entire building is filled with books, except for a quarter of one floor. This space has been allocated to the Boston Medical Library and will be fitted with metal stacks built close together in eleven and a half double-faced ranges. A range consists of nine sections 3 feet in width, making a total of 27 feet in length, and each section contains seven, eight or nine shelves, depending on the height of the books. The total number of linear feet available for shelving is about 2000, and on an estimate of eight or nine volumes to a foot, the space will accommodate about 20,000 books. Thus, the little-used material will be available either at the Deposit Library itself or for daily transportation back to the Boston Medical Library. Books and other material designated for the New England Deposit Library will be moved after July 1, for this material has already been partly earmarked and a considerable portion is segregated in boxes piled on top of the present two tiers of stacks in the new stack building. Some books, moreover, will be removed from the old stack room, and by the use

of the Deposit Library, even though our new stacks are not built within a year or two, the Library will be in reasonably good condition so far as shelving in the immediate future is concerned.

What should be the aim of the Boston Medical Library in the future? It cannot continue to develop as a universal medical library, for it has neither the space nor the money. The Library must change its course without, in general, changing the principles for which it was founded. Book-collecting activities should be delimited, and the Library developed into a first-rate working research collection, rather than a universal collection in the field of medicine. Delimitation should be based on three aims certain aspects in book collecting in which the Boston Medical Library should have a strong or inclusive collection, those in which a good up-to-date representation is sufficient, and those in which a comparatively small sampling is all that is needed. The first category consists of strong groups of current medical journals in all languages and from all countries. We should receive more than a thousand current medical periodicals, and provision should be made to bind and house them conveniently on our shelves. In addition, the latest textbooks, monographs and current editions of all sound medical publications should be acquired, particularly in the field of clinical medicine. In the second category, the fields allied to medicine, we should have an up-to-date representative collection of books on chemistry, physics, biology and so forth. We should not expand completely into this field, for books of this type are available at other libraries in or near Boston. Through a mutual understanding and interlibrary loan system, volumes called for in these categories could easily be obtained for our readers. Finally, we need a sampling of the greatest books in medical history. Many of these have already been acquired by the Library, but we should keep up our strong collection of medical history, biography, bibliography, literary medicine, reference books and similar branches so far as our funds permit. There is no reason, moreover, why the Library should not welcome more funds for such a purpose, and the Librarian will certainly not look askance at a medical library of historical interest to supplement the collection along these lines. This, however, would not be the primary interest, and the Librarian does not contemplate turning the Boston Medical Library into an antiquarian society. Because of the impetus given to it in the past, however, because of funds already acquired and because of forces that bring things to a library so well housed and catalogued as ours, he does not worry about the continued care and augmentation of our special collections. Such books are, indeed, the working tools of the medical historian. As scholars learn about our collection of incunabula and other books of rare and important value, the Library becomes more and more used every year for his-



torical research. We are thus attempting to suit the working needs of the scholars of medical history as well as to supply all the needs of the members of the medical profession in Boston and in Massachusetts. Everyday working purposes should set the standards, however, rather than inclusive historical or bibliographic ends.

In addition, we need a weeding-out process. The Library should have had in years past what Osler always termed "an annual shed." Unfortunately, the Boston Medical Library has been primarily acquisitive for over seventy-five years, taking nearly all it could put its hands on and being rather proud of the growing collection. During this process we have not unnaturally added a certain amount of nonmedical material that should be discarded at once, and similar items should not be acquired in the future. Borderline material may be kept by the Library and deposited in the New England Deposit Library, where it is easily accessible when called for.

#### RELATION WITH THE MASSACHUSETTS MEDICAL SOCIETY

The Library building has long been the headquarters of the Massachusetts Medical Society as well as the repository for our collection. In it are housed the offices of the Society and of the *New England Journal of Medicine*. That these organizations should seek a closer form of co-operation with the Library is not surprising, for the added support of the Massachusetts Medical Society to the Boston Medical Library will give to the medical profession in Massachusetts a proper solidarity not found in any other state in the Union except possibly in Maryland, where the Medical and Chirurgical Society maintains its own library in its own building. Thus, an opportunity is given to interweave the old with the new. All the records of the Massachusetts Medical Society, the early documents pertaining to medicine in the Commonwealth and items of every description regarding the practice of doctors and the lives that they led have already accumulated in abundance in the Boston Medical Library. For over seventy-five years, the Library has been the natural source for the collection and cataloguing of material, and by a gravitational process the libraries of physicians have been bequeathed in large numbers to the Library itself, thus, we have on our shelves a reflection of the past practice of medicine in Massachusetts, a portion of which has already been used in the *History of the Massachusetts Medical Society* and similar publications. The Library will continue to add everything that is pertinent to medicine in Massachusetts, for not only from books but also from manuscripts and private letters of our predecessors can a vivid picture of their lives and the times in which they lived be formed.

To these must be added the old books in medicine, for as Osler said, "Nothing utilizes the new more

effectively than the presence of the old." Our special collections give the same tone to the Library as the portraits of ancestors by Stuart and Copley to the dining rooms of many houses. To the Librarian, all books are old, for nothing ages so quickly as a book. In a decade almost every medical book becomes, indeed, extremely old, and much of the immense literature of the past is not worth shelving, except for historical research, in the Boston Medical Library. We can be grateful that there is an institution in America, the Army Medical Library in Washington, where everything pertaining to medicine can be kept. There is the duty of indiscriminate purchase, ours must be limited to a smaller field, primary consideration being given to the current literature and papers of local interest. Of course, we have had our enthusiasts, who are still welcome and who, for one reason or another, are attracted to a certain class of works, such as incunabula and books on special subjects. Money has been left to us for the purposes of developing these collections, and the Library will never forget its duty. Boston has always had many physicians with the happy combination of literary tastes, leisure and a long purse, and the Library collection reflects the interest of these men as do few libraries of medicine in the United States. Sometimes these interests are expressed in the field of medical medals, portraits, autographs, etchings or bookplates. Here again we should "hold fast to that which is good," for this sort of activity is far from making the Library a dumping ground for unwanted material. There is plenty of that, published mostly in the Seventeenth and Eighteenth Centuries, and the universal collection of material of this type does not fall into our province.

The Library is primarily an educational institution, devoted to the education of the doctor of our time. Every book and pamphlet on our shelves is of interest to someone, but the greatest use of the Library naturally comes with the current literature of all lands and in this we are, indeed, fortunate in the large number of journals, transactions of societies and reports that we accumulate year by year. With the co-operation of the other libraries in and near Boston the Library expects in the near future to be able to make available for the laboratory worker, the specialist and the general practitioner all the current literature that is worth while. Every book and journal may not find a place on the shelves, but should that work be available in Boston or, indeed, anywhere in the United States, the Boston Medical Library will bring it to the doctor's desk or his laboratory table.

In carrying out this idea, the Librarian held an informal conference with the librarians of schools and hospitals in and near Boston on December 7, 1946, to consider matters of mutual interest. Representatives of the Mt. Auburn Hospital Library, Tufts College Medical and Dental School

Library, New England Deaconess Hospital Library, Treadwell Library (Massachusetts General Hospital), Harvard Medical School Library and its departmental libraries, Harvard School of Public Health Library and the libraries of Boston University School of Medicine, Boston City Hospital, Boston Psychopathic Hospital, Beth Israel Hospital, Newton-Wellesley Hospital, Massachusetts College of Pharmacy, Massachusetts Department of

that will benefit all the libraries participating in this conference

### ACCESSIONS

The Library has added two medical manuscripts, a number of Sixteenth Century and Seventeenth

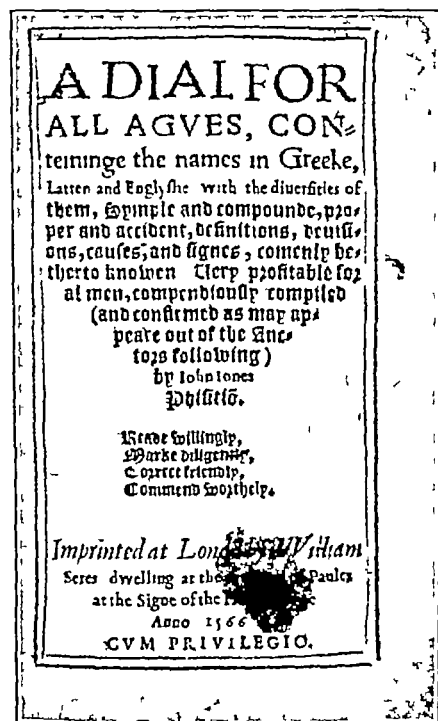


FIGURE 1 Title Page of *A Dial for All Agues*, by John Jones (London 1566)

Public Health and Massachusetts Department of Mental Health met to discuss policies of inter-library loans, the coverage of special fields, exchanges between Boston libraries, the collection of ephemera and related materials and general co-operation regarding the development of the libraries in Boston and its vicinity with special reference to medical, dental and pharmacologic problems. Further meetings of this nature are planned, and there already has been set up a plan for activities

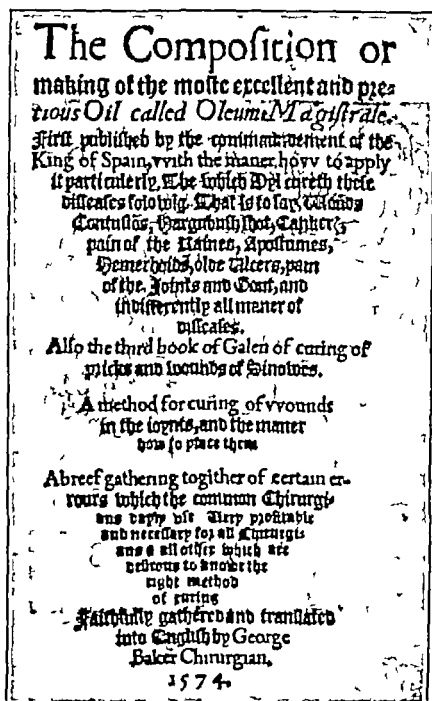


FIGURE 2 Title Page of *The Composition or making of the most excellent and precious Oil called Oleum Magistrale* by George Baker (London, 1574)

Century imprints and eight English books, published before 1640. A fine collection of private letters written by Dr Ezekiel D. Dodge, and a dozen or more American imprints have also been acquired, including the second edition of *Morton's Letheon* (1846).

Two of our English imprints were acquired through the courtesy of Mr William A. Jackson, of the Houghton Library. *A Dial for All Agues*, by John Jones, a Welsh physician, was published in London in 1566 (Fig 1). Dr Jones wrote a number of books on fevers, medicinal baths and general health measures. He was a fashionable physician of his

time who practiced in Bath and other parts of England. The title page contains the following quaint admonition "Reade willingly, Marke diligently, Correct friendly, Commend worthely" Other copies of this rare black-letter book are

This active surgeon also translated the works of Conrad Gesner, Guido and Vigo into English. He was a friend of Clowes, the great contemporary surgeon, and of Gerard, the herbalist. Baker is best remembered for his work in writing on learned

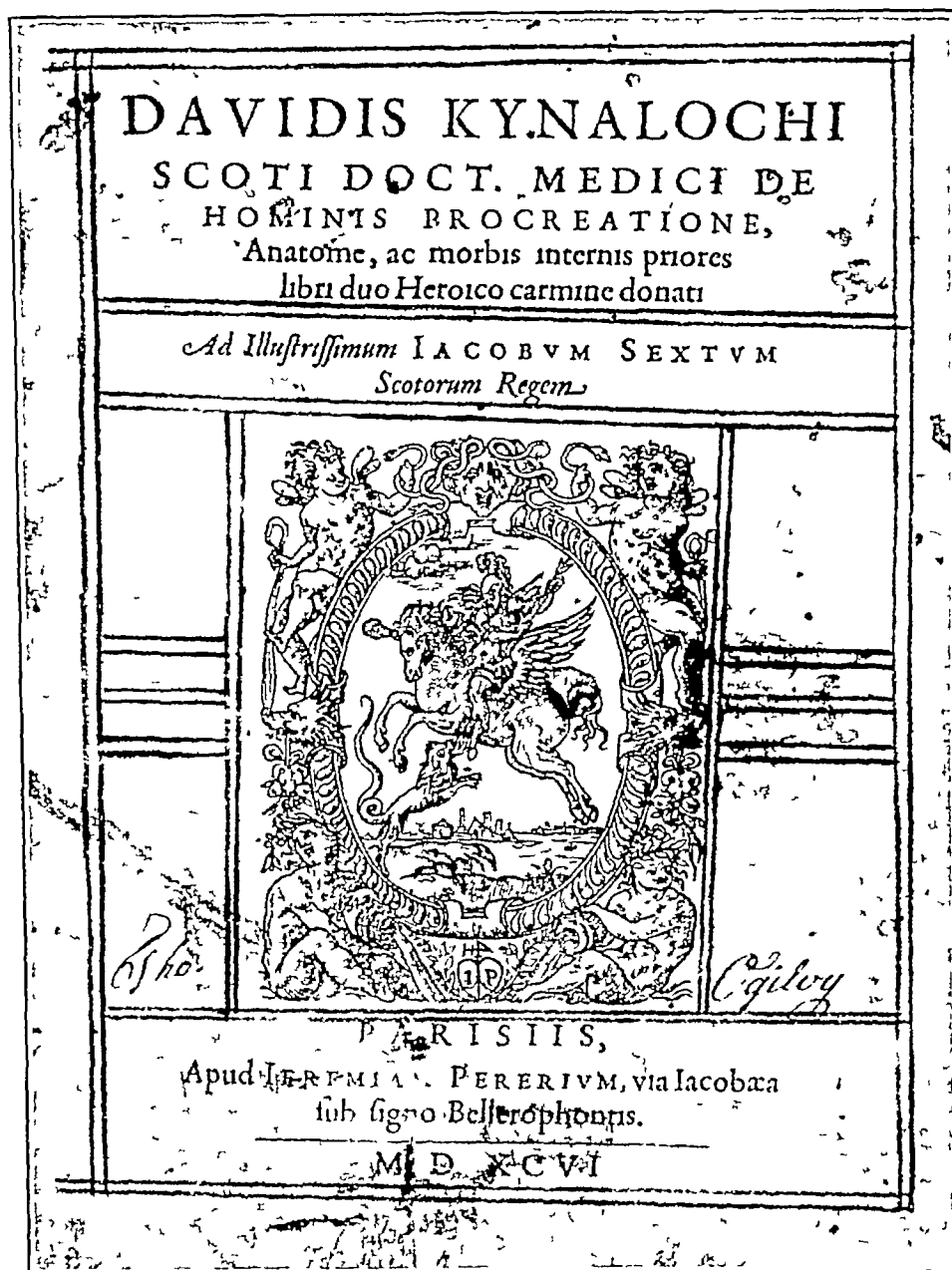


FIGURE 3 Title Page of *De Hominis Procreatione*, by David Kinloch (Paris, 1596)

recorded in the British Museum and the H. E. Huntington Library.

The second book, *The Composition or making of the most excellent and pretious Oil called Oleum Magistrale*, by George Baker, was issued in London in 1574 (Fig. 2). Baker, a member of the Barber Surgeons' Company, was attached to the household of the Earl of Oxford when he wrote on the *oleum magistrale*, a preparation of wine and herbs used for the cure of wounds, ulcers and other diseases.

subjects in the vulgar tongue. Copies of Baker's *Oleum Magistrale* are recorded in the British Museum and Cambridge, England, but not in America.

A third work is a medical poem by a Scottish physician, David Kinloch, *De Hominis Procreatione*, published in Paris in 1596 (Fig. 3). The book is an early text on obstetrics. Little was known of Kinloch until the investigations of R. C. Buist<sup>1</sup> in 1926 disclosed that the author of these Latin verses was born in Dundee in 1559 and probably obtained

his medical degree in Paris in 1596, the year that his book was issued. Like many of his contemporaries, Kinloch was a great traveler. Tradition has it that when in Spain he was seized by the Inquisition and condemned to die. When the Grand Inquisitor became ill, Kinloch's services as a doctor were accepted, and after a cure had been effected, Kinloch was sent home to Scotland.

Finally, a pleasant edition, in Italian, of one of the most popular medical books ever written, *Thesaurus Pauperum* di messer Pietro Hispano, printed in Venice in 1531, was added to our collection (Fig. 4). Of the incunabula editions of Peter of Spain's famous compilation, five in Italian and one, the first, in Latin, only single copies are usually recorded in libraries throughout the world. The Boston Medical Library has the fourth edition in Italian, the only example of this printing in America. Some of the other editions, including the first Latin and the first Italian, are available to American scholars in the Army Medical Library. After 1500, more frequent printings of the *Treasury of the Poor* were demanded, since it had become the most popular book of its kind in the Sixteenth Century. This was at least partly due, as Sarton reminds us, to its brevity and to its practical nature. In addition to the 1531 Italian imprint the Library has the first printing in English, issued in London about 1550, and the first Spanish edition of 1532. The title page of the *Thesaurus* of 1531 shows a patient presenting to the physician a bottle of urine for diagnosis. The doctor in turn gives to the patient the appropriate diagnostic slip from a stock of them in a bag at his feet. Peter of Spain — or more accurately, Peter of Portugal, since he was born in Lisbon — was the son of a physician. He studied medicine in Paris and Siena, became a cardinal in 1273 and Pope John XXI in 1276, only to die by accident eight months later. Peter also wrote a treatise on diseases of the eye, many commentaries and a book on logic.

#### LIBRARY ACTIVITIES

##### Exhibits

The Library took part in a number of important exhibits in 1946. A special exhibit in the Whitney Museum of Modern Art in New York in October and November and also a continuation of this exhibit at the Museum of Fine Arts in Boston was augmented by our collection of drawings by Dr. William Rimmer. During the centennial of the First Public Demonstration of Ether Anesthesia, held primarily at the Massachusetts General Hospital on October 16, 1946, the "Ether Painting," by Robert Hinckley, which hangs in Ware Hall, was restored, prior to the exhibit at the hospital, through the kindness of our former president, Dr. David Cheever. The most significant parts of our ether

collection were on exhibit in the Treasure Room at the Boston Public Library during October and November.

##### Gifts

The Library has received many special gifts through the kindness of a wide variety of individuals

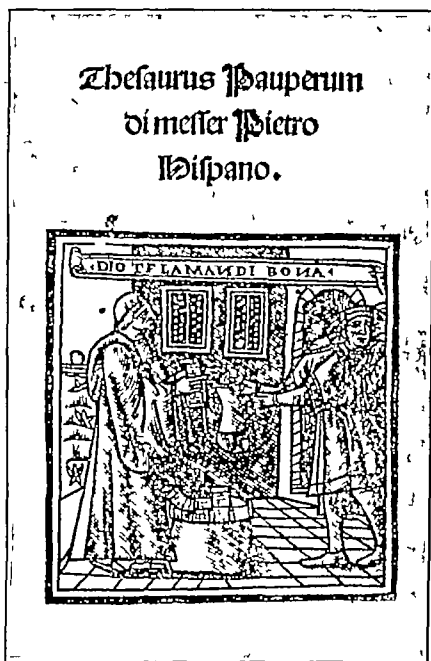


FIGURE 4 Title Page of *Thesaurus Pauperum* by Pietro Hispano (Venice 1531)

and libraries. Particularly valuable is a collection of French theses and Dutch and Spanish dissertations received from Harvard Medical School. The Suffolk District Medical Society made a grant of money to the Boston Medical Library in the sum of \$1350. Dr. David Cheever presented a substantial sum for the purpose of restoring the Hinckley picture, and Dr. Dwight O'Hara gave money to encourage the use of the meeting halls in the Boston Medical Library by student organizations.

##### Meetings

The Director attended a meeting in honor of Miss Marcia D. Noyes, long the librarian of the Medical and Chirurgical Faculty of the State of Maryland, the meeting of the Medical Library

Association held in New Haven, Connecticut, and a meeting of the Honorary Consultants of the Army Medical Library, in Washington. The last meeting was also attended by the Librarian.

### Book Reviews

The Library is rapidly getting up to date with book reviews and book notices. These fell behind in the early part of the year owing to the absence of many reviewers in the armed forces and the shortage of space in the *New England Journal of Medicine* for their publication. Toward the end of the year an active endeavor was made to bring this matter up to date, and by the beginning of 1947 the situation was greatly improved. Reviews of some books were not published in the *Journal* for over a year after receipt. It is now expected that reviews, or at least notes on books, can be published within two or three months after the receipt of the item by the *Journal*. Much of this depends on the good will of our reviewers, who should act promptly or return the book to the Library if they are unable to review it. Secondly, an effort is being made to publish reviews promptly in the *Journal*. The paper shortage, however, is still acute, and the editor reports that it may not be possible to find space to publish all the reviews as promptly as desired.

### Publications

Recent articles emanating from the Library are as follows:

*Seventieth Annual Report of the Boston Medical Library for the Year 1945* 40 pp. Boston privately printed, 1946.

Viets, H. R. Nathan P. Rice and *His Trials of a Public Benefactor*, New York, 1859. *Bull Hist Med* 20:232-243, 1946.

Editorial. First description of rickets. *New Eng J Med* 235:144, 1946.

Cheever, D. Boston Medical Library. Report of the President. *New Eng J Med* 235:709-711, 1946.

Viets, H. R. Boston Medical Library. Report of the Librarian. *New Eng J Med* 235:711-717, 1946.

Editorial. Bigelow's original announcement. *New Eng J Med* 235:769, 1946.

Ballard, J. F. *Boston Medical Library Medical Classification*. Part Two—Index. Third edition, revised. 97 pp. Boston privately printed, 1946.

### VARIA

We were pleasantly reminded of some chapters in the history of the medical school at Cambridge by the late Sir Walter Langdon-Brown,<sup>2</sup> who revived our interest in John Caius, William Gilbert, Francis Glisson, William Heberden, Clifford Allbutt and their contemporaries in a series of brilliant papers delivered before the History of Medicine Section of the Royal Society of Medicine and now issued in book form.

Professor G. Grey Turner<sup>3</sup> retold the history of the Hunterian Museum at the Royal College of Surgeons of England, and for the first time in detail we learned of the tragic bombing and fire of May 10, 1941, with the loss of many treasures, leaving the main rooms of the building a hollow shell. About two thirds of the total collections were destroyed, but fortunately many of the original Hunter specimens survived along with the great life-size statue of Hunter, which had been encased in stout brickwork. It is cheering to know that the museum will be reconstructed and that John Hunter's work will still be a source of inspiration to medical men throughout the world.

From a sister institution, the Royal College of Physicians of London, comes the belated FitzPatrick Lectures, planned but not delivered in November 1939, and now printed by the College. The story of the medical interchange between the British Isles and America before 1801 was delightfully told by Archibald Malloch,<sup>4</sup> librarian of the New York Academy of Medicine, in a series of chapters devoted to various regions of America, such as the West Coast, the Colonial States, the West Indies, the Maritime Provinces and Canada. A valuable chapter deals with medical books reprinted in America before 1801.

HENRY R. VIETS

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- 3 Turner, G. G. *The Hunterian Museum Yesterday and To-morrow. Being the Hunterian oration for 1945. Delivered at the Royal College of Surgeons of England*. 87 pp. London: Cassell & Co., 1946.
- 4 Malloch, A. *Medical Interchange between the British Isles and America before 1801. Based on the FitzPatrick Lectures of the Royal College of Physicians of London for 1939*. 143 pp. London: Royal College of Physicians, 1946.

## CLINICAL NOTE

## SOLITARY UNICAMERAL CYST OF THE OS CALCIS

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A REVIEW of the literature reveals a surprisingly low incidence of solitary cysts of the os calcis. The most recent report is that of Copelman et al.<sup>1</sup> Only 12 cases are recorded in the literature, of these only 4 were reported by American physicians. The patients in Copelman's cases complained of pain on standing or walking, which was also the complaint in the case presented below. The case

had been in the military service and was receiving disability for bilateral pes planus. He complained of aching in both feet, and there were clinical objective signs of marked relaxation of the longitudinal arches of both feet, as well as extreme pronation of both feet that was more marked on the left.

Röntgenographic studies of both feet in the lateral projections—on weight bearing—revealed a low triangular pattern produced by the head of the metatarsal and calcaneus. A large cystic lesion was observed in the left os calcis that measured 3.5 cm in diameter (Fig. 1). The lesion was large with a sharply marginated radiolucent area involving the anterior half of the os calcis. This lesion was of a pyramidal shape, lying parallel with the long trabeculations of the posterior half of the bone. The posterior segment of the cyst extended superiorly as high as the sulcus for the flexor hallucis longus, anteriorly as far as the trochlear process, posteriorly as far as the lateral process of the os calcis and inferiorly as far as the cortical portion of the plantar surface of the bone. The trabeculations of the cystic segment were ill defined, whereas the trabeculae of the posterior half of the calcaneus appeared normal. The cyst seemed to abut on and to expand the inferior and lateral cortex.



FIGURE 1

described by Smith<sup>2</sup> was believed to be either osteitis fibrosa or a peculiar architectural anomaly. Brailsford<sup>3</sup> described a lesion of the os calcis that was identical in appearance with that in the case reported below. Brailsford called the lesion a "triangular area of osteoporosis." Jaffe and Lichtenstein's<sup>4</sup> survey of the records of the Hospital for Joint Diseases from 1925 to 1942 failed to reveal a single case of solitary unicameral cyst of the tarsal bones analogous to the type that occurs in long tubular bones.

## CASE REPORT

A 28-year-old man was referred for roentgenographic studies of the feet in weight bearing position. This patient

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Solitary cyst of the calcaneus occurs in the same location in every case reviewed—that is, on the anterior, inferior and lateral aspects of the bone. The cyst is of the single type, with a well defined wall.

The appearance in all published cases is identical, but the lesion in the case reported above is probably the largest encountered.

## SUMMARY

A single case of solitary cyst of the calcaneus is presented, adding to the 12 cases already reported in the literature.

The cyst always involves the anterior half of the os calcis

As in other cases, the patient complained of pain on walking or standing

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## MEDICAL PROGRESS

### TUBERCULOSIS

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THE prolonged and chronic course characteristically pursued by tuberculosis is reflected in the slow progress that is being made in its conquest. The fatty armor that encapsulates the tubercle bacillus has only been dented, not destroyed, by man-made devices. Until some chemotherapeutic or antibiotic agent is found that will penetrate the inner defenses of this hardy microbe, progress in the field of tuberculosis will continue to resemble a series of skirmishes rather than a pitched, decisive battle.

#### CHILDHOOD TYPE

A clearer concept is developing concerning the so-called "childhood type" of tuberculosis and its relation to tuberculin sensitivity and pulmonary calcifications. Although it has been amply demonstrated in recent years that not all calcifications are due to tuberculosis, the question remains unanswered whether there is a loss in tuberculin sensitivity following the healing of known primary tuberculous lesions. If the primary complex is truly healed, does the child become tuberculin negative? If not, how long does tuberculin sensitivity persist?

To answer these questions Hardy<sup>1</sup> reviewed the records at the Harriet Lane Home Tuberculosis Clinic and selected 312 subjects (born between 1912 and 1930) who had had a primary tuberculous infection in childhood and who had been followed for at least seven years. In this group there were 193 Negroes and 129 Whites. All had had at least one positive tuberculin test, and 87 per cent had known contacts. Follow-up examinations revealed that tuberculin sensitivity was remarkably persistent during the period of study but varied considerably with the degree of infection received in childhood. In subjects who had had primary pulmonary infection, there was practically no loss in the degree of sensitivity, whereas of 171 persons who had had primary mediastinal tuberculosis, 2 per cent became anergic. Of the 82 remaining patients who had had only a positive tuberculin test without any associated roentgenologic findings, as many as 6 per cent be-

came anergic. Thus, the greater the severity of the initial infection, the more persistent tuberculin sensitivity appeared to be. Conversely, it is likely that if calcifications are present and the tuberculin test is negative, tuberculosis is not responsible.

Another study, by Edwards and Hardy,<sup>2</sup> reveals that the degree of tuberculin sensitivity bears some relation to the prognosis. In 34 children who were relatively insensitive—that is, with reactions to not less than 10 mg of tuberculin before their third birthday—there were no deaths, and no patients developed pulmonary calcifications or extrapulmonary lesions. There were no deaths in a group of 26 children who reacted to 0.1 mg of tuberculin, but 3 patients showed subsequent calcifications on x-ray examination of the chest. In sharp contrast, in the highly sensitive group of 103 children who reacted to 0.01 mg of tuberculin, 43 per cent had noncalcified parenchymal lesions, 62 per cent developed intrathoracic calcifications and 14 per cent died. Of 44 infants who gave vesiculate reactions to 0.1 mg of tuberculin, 50 per cent developed parenchymal lesions, 77 developed intrathoracic calcifications and 16 per cent died. Thus, the degree of sensitivity in childhood may serve as a rough guide to the prognosis—the less sensitive the response, except, of course, in moribund patients, the better the prognosis.

The age of the patient at the time of infection also seems to bear a significant relation to the prognosis. The opinion of Kendig and Hardy<sup>3</sup> is as follows:

The infected infant may be able to overcome tuberculous infection if the adult contact can be promptly removed. If, however, the contact remains and the baby is subjected to a constant opportunity for more infection, there is much greater likelihood of a serious, or even fatal, outcome.

It is wise to assume, therefore, that all subjects who show a positive tuberculin test before the age of three years have active infection. In such children, indeed, the infection has hardly had time to become inactive. More light on these problems may eventually be shed by the plan of study suggested by

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Biggs,<sup>4</sup> in which x-ray and clinical investigations are correlated

Arrest of disease in childhood, as indicated by a calcified primary complex, may denote a truly healed lesion in the sense that the calcified lesions are no longer infective. To determine how frequently viable bacilli could actually be recovered from the primary complex of children dying of other causes, Feldman and Helmholz<sup>5</sup> collected material from 29 cases over a period of six years and inoculated the specimens into guinea pigs. In only 5 cases were viable, virulent tubercle bacilli demonstrated by the tests. The authors state

The failure to demonstrate the presence of living tubercle bacilli in 24 of 29 patients having childhood tuberculosis provides reasons for support of the belief that sensitivity to tuberculin in children may be transitory and that, in children whose tuberculosis is limited to the lesions of the primary complex, the continuation of the sensitivity to tuberculin is probably related to the infectivity of the tuberculous foci.

The age at which infection occurs appears to have a direct relation to the development of calcifications. High and Zwerling<sup>6</sup> studied 198 American-Indian children who developed tuberculosis while under observation and in 49 of whom calcifications later developed. Deposits of calcium were noted one to four years after the appearance of the lesion, usually during the second and third years. More than three fourths of the youngest patients developed calcifications, whereas calcium deposits were detected in only 2.4 per cent of the cases in which the onset of the disease was between the ages of fifteen and nineteen years. The presence of demonstrable pulmonary lesions appeared to influence the subsequent development of calcifications. One fourth of the patients who had pulmonary lesions subsequently showed calcium deposits. On the other hand, in cases in which tuberculin conversion was not accompanied by any demonstrable lesion, calcium appeared in only 2.2 per cent.

Although tuberculosis is extremely serious in infancy, the disease is relatively mild later in childhood. It is also true that the treatment of children with a primary complex, such as that afforded by a sanatorium, has no effect on the development of progressive tuberculosis in later life. Most competent investigators therefore believe that mass examination of children in grade schools should be abandoned.<sup>7</sup> High-school students can be examined more profitably, but, as Pope<sup>7</sup> points out, there is still some controversy regarding whether routine screening by the tuberculin test is desirable. Much, he says, depends on the region in which the tests are being done and on the type of x-ray equipment used. A final diagnosis of tuberculosis, however, should not be made on the first x-ray film, since a disturbing number of cases showing definite infiltrations of the lung fields will be found to have cleared completely on a re-examination two weeks later.<sup>7</sup> Although mass examination of high-school students for tuber-

culosis is popular with parents and school authorities, Pope suggests that general hospitals, industrial plants and mental hospitals are more profitable fields for discovering new cases.

The precise role that should be assigned to the tuberculin test in case finding is still a matter of dispute. Myers<sup>8</sup> has advanced persuasive arguments for routine tuberculin testing of all children, as well as adults, and has cited considerable evidence for its value in controlling tuberculosis in the Minneapolis area. "Twenty-five years ago, the tuberculin test was believed to be only applicable to children, but experience has taught that it is of great value in testing persons of any age." According to his point of view, any person reacting to tuberculin has tuberculosis just as certainly as the patient who is dying from the disease, the only difference being one of degree. Hilleboe<sup>9</sup> has prudently prefaced Myers's statements with the notation that this point of view is at variance with the conclusions of some other workers in the field. Tice,<sup>10</sup> of the Chicago Municipal Tuberculosis Sanatorium, presents a somewhat different approach to the problem.

#### CONTROL

Although the x-ray apparatus detects pulmonary lesions more readily than the stethoscope, chest roentgenology has not yet advanced to the point where it can be substituted for logic or reasoning. Diagnosis is a function of logic, and the diagnosis of chest diseases, especially tuberculosis, depends on the correlation of clinical, roentgenologic and bacteriologic studies. No x-ray machine can do this. The diagnosis of tuberculosis or its degree of activity should never be based wholly on the x-ray report of the chest findings. "Never put your complete trust in shadows" is a sound medical adage that applies especially to tuberculosis.

Probably the most notable advance in the past year lies in the growing awareness of the fallibility of the x-ray machine and its limitations in the diagnosis of tuberculosis. Certainly, x-ray findings, alone, must never be used to determine the disposition of the patient. The chief exponent of this thesis is Hilleboe,<sup>11</sup> whose remarks should be compulsory reading for every physician who has occasion to send a patient to the sanatorium. He contends that many persons have been labeled as tuberculous wholly on the basis of the x-ray findings. "This is scientifically unsound," he says, "and damage is done to people and to control programs." A patient with suspicious x-ray findings should, at least, have a complete history, a physical examination and sputum studies before the x-ray findings are tagged with a specific label. "Let treatment be delayed," urges Hilleboe, "until all the facts are in and all the evidence is evaluated." Persons who have tuberculosis that requires sanatorium care cannot be greatly harmed by a short delay of treatment, in many cases the disease has been present



for some time. Even those whose diagnosis is confirmed will profit by a period of waiting, during which they may become accustomed to the idea of having a serious disease. Similarly, in my opinion, the sending of a person who does not have tuberculosis to a sanatorium is tantamount to imprisonment without a fair trial. Worse still, it may expose a susceptible person — especially one who is tuberculin negative — to possible infection.

Other authorities agree that clinical conclusions drawn hastily from x-ray films are dangerous. A recent exhaustive report<sup>12</sup> emphasizes the fact that the personal equation enters significantly into the interpretation of chest films so that one man may read tuberculosis on a film at one time and may call the same film normal when it is reviewed.<sup>12</sup> The variation in interpretation among several observers is even greater. Shepard<sup>13</sup> also cautions against overlooking some of the limitations of the mass x-ray survey.

We should not refer to the x-ray as the one and only way to diagnose tuberculosis. Even 14-by-17-inch stereoscopic plates will not provide a sure diagnosis, much less a single miniature film. Positive diagnosis of tuberculosis is a long, complicated, highly skilled process. The x-ray is but a part of this process.

All the roentgenologist can and should do is to describe the type of shadows cast on the film, since shadows identical with those of tuberculosis may be cast by many diseases. Diagnosis should rest with the clinician, not the roentgenologist. In this connection, Rest<sup>14</sup> has cited many cases in which nontuberculous pulmonary conditions have been diagnosed as tuberculosis on the basis of the x-ray and the clinical findings. In every case, however, examination of the sputum was negative.

If there is so great a liability of diagnostic error in the routine mass x-ray surveys and even in the standard 14-by-17-inch films, it is difficult to understand how miniature photofluorography of the clothed subject can fail to add considerably to the existing confusion. Nevertheless, the experience of Lewis<sup>15</sup> indicates that, for mass surveys only, photofluorography of the clothed subject is without objection and that it has the advantages of speed of operation and reduction of space and personnel. Lewis, however, admits that this approach to the problem may be productive of a "narrow margin of error."

The general practitioner has often been glowingly referred to as the "keystone" in any tuberculosis-control program and, at the same time, has often been criticized for failing to put the full weight of his authority behind government-planned surveys or other publicly sponsored control measures. Too often, according to Hilleboe,<sup>16</sup> the control of tuberculosis is assumed to be the responsibility of the health department alone. Yet how can the assumption be otherwise when more and more of the physician's responsibility of diagnosis and treatment is being taken over by public-health authorities? How

often, indeed, is the general practitioner asked to sit in the councils where tuberculosis programs are planned? Neither the state agencies nor the voluntary agencies seem to look to the practitioner for an opinion.

During the past decade or two, it seems to me, there has been a progressive narrowing of the opportunities available to an intern or resident — the future practitioner — to acquaint himself with the diagnosis and management of tuberculosis. General hospitals often prohibit the admission of tuberculous patients. Other hospitals provide only interim care until admission to a sanatorium can be arranged. As a result, training in tuberculosis is often inadequate and a quasi-conditioned reflex has been created among physicians so that the mere mention of the word "tuberculosis" carries an instantaneous connotation of "sanatorium." Lack of responsibility in the care of these patients during the period of training gives the physician a sense of insecurity both in diagnosis and management. Consequently, it has been necessary recently for public-health authorities to compile a guide for the physician in the disposition of persons with abnormal x-ray findings.<sup>17</sup> As valuable as this guide is, it is no substitute for the confidence gained from experience that a physician should have in the handling of all patients. To the dictum of Hilleboe and Holm,<sup>17</sup> "Do not diagnose pulmonary tuberculosis on the basis of an original x-ray film alone," should be added the corollary, "Not every patient with tuberculosis has to be in a sanatorium." Practically, all such patients can be studied at home, and some, if conditions are favorable, can be treated under the general practitioner's care with, perhaps, occasional advice from an expert. Only then will the general practitioner be an active participant in tuberculosis-control programs.

In spite of these considerations, it is gratifying to report the continuing decline of tuberculosis mortality. To those interested in some of the statistical aspects of tuberculosis control, the reports of Pitney and Kasius<sup>18, 19</sup> are recommended. The world-wide situation regarding tuberculosis prior to the war is briefly discussed and summarized by Yelton.<sup>20</sup>

#### BACTERIOLOGIC CONSIDERATIONS

Dubos and his associates<sup>21, 22</sup> have continued their researches on the growth of tubercle bacilli. Although tubercle bacilli are among the least exacting of pathogenic micro-organisms in their growth requirements, it is often difficult to initiate the growth of small inoculums in vitro. Furthermore, multiplication may be slow, even in some enriched mediums. Dubos and Davis<sup>21</sup> make the following observation:

These characteristics render difficult the application to tubercle bacilli of a quantitative bacteriological method based on enumeration of living cells by plating or dilution techniques, they delay and at times prevent bacteriological diagnosis of tuberculosis, they hinder investigation concerned with pathogenesis, immunity, and chemotherapy.

Any technic providing for rapid growth and growth of small inoculums would therefore benefit many fields of investigation

Such a technic appears to have been devised by Dubos and Davis,<sup>21</sup> who describe a modification of Kirschner's medium that is easy to prepare, as well as stable, and favors the growth of small inoculums. In such a medium, the growth-stimulating effect of certain synthetic water-soluble lipids—consisting of esters of long-chain fatty acids—is readily demonstrated. All these stimulating compounds possess both lipophilic and hydrophilic properties, and of these, the product marketed as "Tween 80" (the water soluble ester of oleic acid) was found to be the most satisfactory and the most reliable in its behavior. In the presence of such water-soluble esters the mycobacteria grow diffusely throughout the liquid medium rather than as a surface pellicle. Most important to the clinician is the fact that positive human sputums—after treatment with sodium hydroxide— inoculated into such mediums yield typical diffuse growth. Significant, too, is the fact that high agglutination titers for these new types of culture have been observed in some human serums.<sup>22</sup> The usefulness of these researches in the study of the immunologic response in tuberculosis is apparent.

Further investigation along some of the lines indicated above has been carried out by Foley<sup>23</sup> and Youmans.<sup>24</sup> At the Massachusetts General Hospital, Foley utilized the depth-growth technique for recovery of tubercle bacilli in the examination of pathologic material sent routinely to the laboratory. An excellent correlation was obtained between the cultural results and those found on guinea-pig inoculation, especially when a small amount of human or bovine serum albumin was added to the culture medium. The incubation period in these cultures ranged from five to twenty-seven days, with a mean of eleven days, in sharp contrast to the period of eight to twelve weeks often required for diagnosis by guinea-pig inoculation. "This preliminary study," comments Foley, "suggests that with reasonable care in their use, these new synthetic media can be invaluable in the laboratory diagnosis of tuberculosis."

Youmans,<sup>24</sup> on the other hand, has used depth-growth technique not for diagnosis but to study the culture cycle and growth rate of the tubercle bacillus. The growth curves so obtained showed either a lag phase, such as that obtained with other bacteria, or curves of direct growth not preceded by any lag. Such curves are especially valuable in that they afford the investigator a method for determining the degree of inhibition of various bacteriostatic substances. For example, by this technic it could be demonstrated that, in suitable concentrations, para-aminobenzoic acid could reverse the bacteriostatic action of 4,4-diaminodiphenylsulfone. On the other hand, para-aminosalicylic acid appeared to be

highly bacteriostatic *in vitro* and at least moderately effective for the suppression of tuberculous infection in white mice.<sup>25</sup>

An interesting sidelight to the bacteriologic diagnosis of tuberculosis lies in the fact that false acid-fast organisms may be obtained from some wounds to which fats and greases, such as lanolin and petrolatum, have been applied. Saprophytic diphtheroids present in the wound may become coated with such fats, presenting an almost typical acid-fast appearance when stained by the usual methods and viewed under the microscope.<sup>26</sup> The nature of the acid-fast stain itself has been further elucidated by Lamanna,<sup>27</sup> who postulates that the basis for the acid-fast property lies in the greater solubility of the phenol and dye in the cell constituents than in the decolorizing agent.

### THERAPY

#### *Antibiotics*

Unlike other chemotherapeutic agents and antibiotics that have had their day of popularity and have quickly gone into discard, streptomycin continues to be a drug of promise in the treatment of tuberculosis. Although Corper and Cohn<sup>28</sup> believe that, on the basis of experiments *in vitro* and *in vivo*, there is no evidence that streptomycin enters the important organs in appreciable amounts for any significant time and that the drug is not tuberculocidal in reasonable amounts, they also believe that this antibiotic does retard the growth of actively multiplying tubercle bacilli. "In the usual case of clinical tuberculosis in man, the bacilli appear to reproduce and develop only at irregular periods undeterminable by clinical means and over long periods of time, and this markedly reduces the applicability of a retardant without tuberculocidal action for use in human tuberculosis." Although its application to human tuberculosis is therefore limited, streptomycin may indicate the selective tuberculocide through laboratory experiments.

Clinical reports, however, indicate that streptomycin is effective in the control of tuberculosis. Hinshaw and his colleagues,<sup>29</sup> in a study of 75 tuberculous patients, report that the drug has a "suppressive action" in man but add that long study will be required to determine its optimal dosage and the duration of treatment in various clinical situations. Of 10 patients with generalized hematogenous tuberculosis with or without meningitis, 4 (with meningitis) recovered after streptomycin therapy, clinical findings, however, indicated that the infection had persisted, and the long-term prognosis appeared uncertain. Of 24 patients with pulmonary tuberculosis—14 far advanced, 8 moderately advanced and 2 minimal—19 improved with sufficient promptness to make it appear probable that treatment with streptomycin was a significant factor. All of 6 patients with ulcerating lesions of the major respiratory passages responded rapidly to a com-

bination of streptomycin aerosolization and intramuscular injections. On the other hand, only 8 of 14 patients with urogenital tuberculosis gave a favorable response to treatment. In most cases the total daily dose varied from 1 to 3 gm.

Pfuetze et al.<sup>30</sup> also report a series of 30 cases of pulmonary tuberculosis in which streptomycin was administered from two to six months. With few exceptions the patients selected for antibiotic therapy had tuberculosis that was progressive or had not responded to rest in bed. Of these 30 cases, 20 were far and 8 moderately advanced, and in 2 the disease was minimal. On the basis of roentgenographic findings, there was marked improvement in 13 cases, moderate improvement in 7 and no change in 4. Within three to six months after the administration of streptomycin had been stopped there was some exacerbation of the disease in 7 cases, indicating that the action of streptomycin was merely suppressive, not tuberculocidal. In a case of tuberculous meningitis reported by Krafchick<sup>31</sup> complete clinical recovery was obtained with absolutely no residual neurologic abnormalities.

Some of the limitations of antibiotic therapy have recently been outlined by Hilleboe<sup>32</sup> as follows:

It should be kept in mind that any antibiotic, even though effective against the tubercle bacillus, may be of little benefit to far-advanced cases, because irreversible processes have set in and, in most instances, the blood supply to areas of cavitation and other areas with extensive involvement has been cut off.

Too much help should not be expected from an antibiotic in such advanced cases, even though its action is most favorable in minimal disease.

Some other antibiotic, or a combination of an antibiotic and chemotherapy, may prove ultimately to be the actual solution of tuberculosis management. Marshak,<sup>33</sup> for example, has found that California Spanish moss (*Ramalina reticulata*) can be treated chemically to yield a crystalline substance that is nontoxic for guinea pigs and appears to retard the progress of the disease in experimental infections. The possibilities of this compound in human tuberculosis remain to be explored. Smith and his colleagues<sup>34</sup> have adduced experimental evidence that Promin and streptomycin have a synergism that enhances the antituberculosis action of each. The possible value of such a combination of drugs in human tuberculosis is also unknown at present.

### Chemotherapy

A relatively new bacteriostatic agent, glycerite of hydrogen peroxide, has been described by Brown and Slanetz<sup>35</sup> as having tuberculostatic action in a weak dilution (0.1 per cent) and tuberculocidal action in a greater concentration (from 0.5 to 4.0 per cent). After local application in 4 cases to "cold abscesses" of the chest wall and other areas, complete healing was noted in 3 and improvement in 1. Since glycerol,

itself, may inhibit the growth of tubercle bacilli,<sup>21</sup> however, and since cold abscesses occasionally heal spontaneously, controlled trials with this new bacteriostatic agent must be carried out before its role in the therapy of clinical tuberculosis can be ascertained.

The relation between chemical structure and tuberculostatic activity is of fundamental importance for the future development of more effective tuberculocides, but this relation is still not clearly understood. In vitro tests, however, by Youmans and Doub<sup>36</sup> on fifty-nine different sulfone compounds indicate that two para-oriented free amino groups are essential for maximum activity in the diamino-diphenylsulfone grouping. Thus, p,p-diaminodiphenylsulfone is most active compared to compounds in which a methyl group has been substituted for amino or in other compounds in which the amino radical has been transferred to the meta or ortho position. A new class of tuberculostatic substances, unrelated to the sulfones, has recently been described by Feinstone.<sup>37</sup> The parent compound is 5-amino-2-butoxypyridine, but the sodium formaldehyde bisulfite derivative is least toxic. Some strains of tubercle bacilli were inhibited in dilutions as high as 1:100,000,000. The most striking attribute of these compounds is that they appear to be specific for the acid-fast group of organisms and have little inhibitory action on other bacteria.

### IMMUNIZATION

In an earlier review attention was called to the increasing recognition being given to BCG (*Bacillus Calmette Guérin*) as a possible immunizing agent in selected persons.<sup>38</sup> This year, further evidence regarding its possible value has been presented. Obviously, patients who are already infected, indicated by a positive reaction to tuberculin, are not suitable candidates for BCG immunization.

The experience of the National Research Council of Canada with BCG immunization in hospitals and sanatoriums of Canada has recently been recorded by Ferguson.<sup>39</sup> Nurses entering training between 1934 and 1943 were accepted for this study, and in this group, there were 1005 vaccinated subjects, 759 who were initially Mantoux-negative and not vaccinated and 278 young women who were tuberculin positive. Of the vaccinated persons only 9 developed "manifest tuberculosis," — that is, either pulmonary tuberculosis demonstrable by x-ray study or non-pulmonary disease, — an incidence of 0.9 per cent. Of the tuberculin-negative, nonvaccinated nurses, 29, or 3.8 per cent, developed tuberculosis. And of those who were initially tuberculin positive, 3, or 1.1 per cent, had demonstrable disease. Ferguson therefore considered the use of BCG vaccination in the hospital environment to have reduced manifest tuberculosis among negative reactors by three-fourths. Vaccination with BCG was regarded as a safe, practical, convenient and reasonably effective

method of controlling tuberculosis among young women in a tuberculous environment.

In Brazil, where the mortality rate from tuberculosis is about 250 per 100,000 population, the world's most extensive trials with BCG vaccination have been carried out. The Brazilians prefer to use an oral vaccine instead of an intracutaneous vaccine, such as that employed in Canada. More than 340,000 persons have thus been vaccinated, and the results, to date, are regarded as favorable. The details of the program are described by Bueno.<sup>40</sup>

The Danes have also found that BCG vaccination can be carried out safely and effectively. In

## MISCELLANEOUS TOPICS

### Psychosomatics

With the renewal of interest in psychosomatics generally, a revival of interest in the psychosomatic factors in tuberculosis was inevitable. That this is actually a revival and not something new is pointed out by Friedman and his co-workers.<sup>41</sup> At the Bronx General Hospital they studied 100 male tuberculous patients, each of whom was given at least a one-hour interview by a neuropsychiatrist. Family data and personal and social histories were obtained and carefully tabulated and evaluated. On the basis of

TABLE 1 Results of BCG Vaccination in Denmark

GROUP	MEDICAL STUDENTS			OTHER UNIVERSITY STUDENTS		
	TOTAL NO	POSITIVE X RAY FINDINGS ONLY	X RAY SPUTUM	TOTAL NO	POSITIVE X RAY FINDINGS ONLY	SPUTUM
Mantoux positive	936	12	6	1135	5	4
Mantoux negative	322	38	17	541	14	4
BCG vaccinated	112	0	0	63	0	0

Denmark all children who are Mantoux negative and all newborn infants in a tuberculous environment are vaccinated intracutaneously. On converting to a positive tuberculin reaction, these children and infants have been permitted to associate with the source of infection at home. In Denmark, therefore, BCG vaccination has been subjected to a severe test, and its general acceptance in that country has been based on truly critical appraisal. For example, Table 1, based on an article by Holm,<sup>42</sup> sums up some of the experience with BCG vaccination among college and medical students, who, respectively, are considered "especially exposed" and "not especially exposed" to tuberculosis. Both the hazard of placing a tuberculin-negative person in a tuberculous environment and the significant degree of protection afforded by BCG vaccination are demonstrated. The greatest incidence of infection was among the tuberculin-negative persons placed in a tuberculous environment. Although the numbers are too small for statistical conclusions the vaccinated persons appear to be the best protected against tuberculosis. Other evidence for this point of view is provided by the Danish experience on the island of Bornholm, where the number of new cases of tuberculosis in the group from fifteen to thirty-five years of age has been reduced by half since the introduction of BCG vaccination. Holm's conclusion is as follows:

The vaccination gives considerable but not absolute protection. It protects completely against the morbid phenomena accompanying the tuberculous primary infection and it also affords a considerable protection against genuine tuberculosis of the various organs — in particular against phthisis.

this and other information it was concluded that the patients with tuberculosis had many personality traits in common.

These patients showed independence and efficiency which made them normally or better than normally adjusted in their economic, sexual and social spheres. They showed some resentment toward authority. They showed obsessive and compulsive characteristics and were optimistic individuals.

Since these data apply only to a limited group of persons — young men — conclusions regarding the personality make-up of other tuberculous patients are not warranted. The authors, however, make certain useful suggestions concerning how these traits may be directed toward purposeful and healthier channels.

Another interesting study, but one that I regard as carrying psychosomatics too far into the realm of infectious diseases, is presented by Hartz,<sup>43</sup> who tends to link the dyspnea following thoracoplasty to claustrophobia. The article is valuable in pointing out that psychic reassurance after a thoracoplasty — and perhaps after any major operation — may be as valuable as sedatives and narcotics. Even in tuberculosis one should always remember that the patient, not merely his lungs, needs treatment.

### Pulmonary Lavage

Recent reports from Brazilian investigators indicate that pulmonary lavage as a means of recovering tubercle bacilli warrants further investigation. De Abreu<sup>44</sup> has performed such lavages in 150 cases and considers the technic both efficient and safe. Collection of the sputum is carried out in much the

same way as the pharynx is anesthetized for bronchography, and a cough reflex is then promoted "Pulmonary lavage," says de Abreu, "is yet at the beginning of its application. It is a new method which needs long observation to determine definitely its harmlessness and efficiency." Bueno<sup>45</sup> believes that his technic, which is slightly different from de Abreu's, is easier to perform than gastric aspiration but that it should not be employed in a person who has a low vital capacity or is suffering from asthma.

### *Immobilization of Both Lungs*

During the past few years Barach<sup>46-49</sup> has devised a pressure chamber in which a patient may be placed and allowed (perhaps "forced" would be a better word) to breathe while the chest is completely immobilized. In a recent paper the physiologic principles, the technic and the results of this method are reviewed.<sup>49</sup> Of a small group of patients, 2 showed no benefit, 3 had moderate or temporary benefit, and 5 had marked benefit or clinical recovery. Although Barach appreciates the difficulty in evaluating any new therapy for pulmonary tuberculosis, his observation is as follows:

The provision of local lung rest by residence in the immobilizing pressure chamber promotes the process of healing and closure of cavity in some cases of advanced and moderately advanced pulmonary tuberculosis. This favorable response has been observed in cases for whom no other form of treatment was possible or who had been exposed to other types of tuberculosis therapy without benefit.

### *Ambulatory Pneumothorax*

It is perhaps not widely enough realized that ambulatory pneumothorax may be used as a valuable adjunct to other measures for the control of pulmonary tuberculosis. Rest<sup>50</sup> comments on the futility of trying to admit every tuberculous patient into a sanatorium, since there are only 90,000 beds to accommodate the 500,000 known active cases in the United States. If for some reason, a patient cannot or will not be admitted to a sanatorium, ambulatory pneumothorax may be indicated. Good results are reported in a small number of patients who were given this form of therapy, but Rest cautions, "Delay in administering therapy while the patient is still in the treatable stage may alter the prognosis to an unfavorable one and result in years of prolonged sanatorium care for the patient." Tice<sup>10</sup> has reviewed the Chicago experience with ambulatory collapse therapy and has outlined its growth since 1931. He points out that with ambulatory pneumothorax 76 per cent of the patients treated were living, as compared with 39 per cent of the controls. As of January 1, 1945, there were 1600 patients under therapy, 150 under observation for collapse, and 50 under post-treatment supervision. In China, where hospital facilities are woefully inadequate and living conditions wretched, Wright<sup>51</sup> also commented that, although ambulatory pneumo-

thorax was not an ideal form of treatment, there was obviously a great need for the method under such conditions.

### *Bronchography*

Further recognition should be given to the fact that bronchography, which is widely used in the diagnosis of bronchiectasis, may be carried out with safety in tuberculosis. Boyer<sup>52</sup> points out that whereas bronchography should not be used as a routine procedure in tuberculous patients, it is often of value in revealing the source of positive sputum. This is particularly true in cases in which thickened pleura, empyema and thoracoplasty obscure the pulmonary pattern. Reference should also be made to the exhaustive investigations by Dormer and his colleagues<sup>53</sup> on this subject.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M.D., *Editor*

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### CASE 33271

#### PRESENTATION OF CASE

A sixty-one-year-old mechanic entered the hospital because of epigastric pain.

He had apparently been in good health until seven years before entry (two months before the death of his wife), when he began to have episodes of pain in the right and middle epigastric region. He was treated conservatively for several months at a clinic and then sent home with instructions to rest, to stop smoking and to drink milk whenever he had pain. He remained asymptomatic for six months, but when he returned to work and started to smoke again the pain recurred. During the six years before entry he had pain almost daily. It was not entirely relieved by food and was usually worse about two hours after eating. Amphojel and milk were of some benefit. For six months before entry the patient had had gaseous eructations, nausea and occasional vomiting, as well as increased epigastric pain. He also complained of severe

spontaneous epistaxes, which had occurred during the eight months before entry. There had been no hematemeses or changes in bowel movements. The patient believed that he had recently lost weight but did not know how much. He denied drinking alcohol but admitted smoking twelve to fifteen cigarettes a day.

Physical examination disclosed a well nourished patient in no distress. The heart and lungs were clear. The abdomen was tense, with a sense of resistance in the epigastrium and right upper quadrant. The liver edge was percussed two finger-breadths below the costal margin in the midaxillary line. There was no abdominal tenderness.

The temperature, pulse and respirations were normal. The blood pressure was 148 systolic, 90 diastolic.

Examination of the blood revealed a red-cell count of 5,500,000, with 18 gm of hemoglobin, and a white-cell count of 7300, with 68 per cent neutrophils. The urine was normal. A stool was soft, yellow and guaiac negative. The total protein was 7.0 gm, and the nonprotein nitrogen 28 mg per 100 cc, and the chloride 104 milliequiv per liter. The prothrombin time was normal. A blood Hinton test was negative.

A gastric analysis revealed 40 cc of pinkish, mucoid material with no free hydrochloric acid before the administration of histamine. Thirty minutes after histamine had been given 30 cc of similar fluid contained 30 units of free hydrochloric acid. A gastrointestinal series revealed an ulcer crater, 2 cm in breadth and 1 cm in depth, lying along the lesser curvature high in the fundus just below the esophageal orifice. No definite tumor mass was seen about the ulcer. Barium

passed the pylorus without hesitancy, filling a duodenal bulb to normal contour. On the seventh hospital day gastroscopy revealed a reddish, hyperemic area high in the lesser curvature. This area seemed to extend into the fundus but could not be completely visualized. Elsewhere the gastric mucosa appeared normal. No ulcer was seen.

A smear of gastric juice was reported "negative" for malignant cells. The patient continued to have

somewhat long for a neoplasm. It is implied by the history that the onset of difficulties occurred at a time of great psychic stress. The therapeutic regimen prior to hospital entry was apparently poor. It has been my experience that a patient with a peptic ulcer often receives instructions or advice from his physician to take between-meal antacids or food only at times when pain is present. A proper program is obviously one that prevents

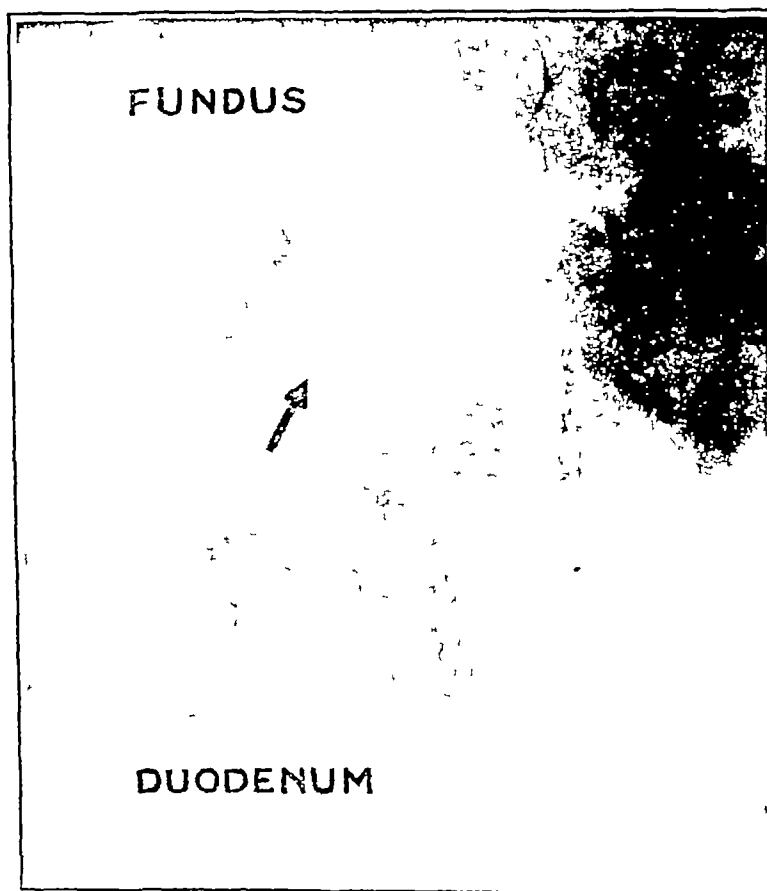


FIGURE 1 *Roentgenogram showing Gastric Ulceration and Surrounding Mass*

pain two to four times in twenty-four hours, usually at night. At times the pain lasted throughout the day and failed to respond to milk and Gelucil. Another gastrointestinal series during the third week showed no change in the size of the ulcer (Fig 1).

On the twenty-seventh hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR WADE VOLWILER: This case presents the problem of the differential diagnosis between benign and malignant peptic ulcer, located high on the lesser curvature of the stomach immediately below the esophageal entrance. The duration of the symptoms, all of which supposedly occurred from this particular lesion, was seven years, which seems

such pain from occurring by regularly scheduling the medication and food by the clock. After a brief remission the pain syndrome in this case returned when the patient returned to work and to smoking. It is entirely possible that tobacco was an important factor in the persistence of this lesion if it proved benign.

I am impressed by the statement that the pain was not relieved by a proper ulcer regimen even after several weeks in the hospital. This fact above all others suggests an infiltrating carcinoma. The gastric analysis in the hospital is of no help in clinical diagnosis.

I should like to know if an x-ray examination of the stomach was carried out at the clinic mentioned

in the record. If so, is it fair for me to have the information?

DR BENJAMIN CASTLEMAN If x-ray examination had been performed, I am sure that the results would have been incorporated in the abstract.

DR VOLWILER Do we have the x-ray films taken here?

DR RICHARD SCHATZKI The report given in the record may be misleading. Usually, the report in the officially prepared record is a statement of fact. Here a conclusion has been drawn. A large crater can be seen on the lesser curvature near the cardia of the stomach extending to the posterior wall. That is referred to in the report as a filling defect around the crater. The question is, Is it a tumor or inflammatory induration around a benign ulcer? Do you want me to give my own opinion? I do not know the case.

DR VOLWILER Why not give it when I have finished? How far below the entrance of the esophagus do you think this lesion is?

DR SCHATZKI I cannot see the actual cardia, but I should say that it was fairly close to it—within a few centimeters.

DR VOLWILER The inner contour of the crater is rather smooth?

DR SCHATZKI Yes.

DR VOLWILER This gastroscopic description leaves something to be desired. The site of an ulcer often cannot be visualized by the gastroscopist. But I should like to know whether peristalsis was active in the hyperemic area described and whether that particular portion of the gastric wall appeared rigid to air insufflation.

DR CASTLEMAN The only additional statement in the gastroscopist's report is that there was no evidence of infiltration.

DR VOLWILER I assume that that means that there was no obvious rigidity.

The Vincent Laboratory here has had a 20 per cent error in diagnosis from examination of fifty gastric-juice samples for malignant cells. An appreciable part of the error is believed to be due to the fact that the specimens are too old and are delivered more than an hour after being drawn from the patient. Better co-operation on our part may improve these statistics. Until the accuracy is considerably higher, this type of examination will not be useful clinically.

I assume that this man was operated on because of two facts that seriously raise the question of cancer: pain continued in spite of good management and was often not relieved by food or antacid, and x-ray study showed little reduction in the ulcer crater during the three weeks' hospital care.

DR SCHATZKI I did not realize that these films were taken on different dates. There is little change in the size of the ulcer, however.

DR VOLWILER Because of the anatomic location of the lesion, I believe that a transthoracic subtotal

gastrectomy was the operation performed. I believe that such an operation in a sixty-one-year-old man in this hospital carries at least a 10 to 15 per cent mortality risk. Is that a fair statement, Dr Welch?

DR CLAUDE E. WELCH It is too high, the mortality for subtotal transthoracic resections being 4 per cent. The percentage for total transthoracic resections for cancer is higher—around 30 per cent.

DR VOLWILER I had not realized that the percentage was so low. Therefore, one needs only to believe that the likelihood of cancer in this patient was greater than 4 per cent if that type of operation was considered to be a proper move. My choice between these two diagnoses can be little more than a guess. I believe, however, that the facts indicate that this was probably an infiltrating carcinoma.

DR CASTLEMAN What is your opinion, Dr Schatzki?

DR SCHATZKI Roentgenologically, the lesion appears to be benign. I cannot tell what the microscope will show.

DR CASTLEMAN The report of Dr Milford D. Schulz was as follows: "The findings are those of gastric ulcer, grossly benign."

DR WELCH I wonder if Dr Volwiler could explain the pain on the basis of the fact that the ulcer had perforated and therefore that carcinoma was not necessarily the cause. I do not argue about the treatment.

DR WALTER BAUER That was my thought, also.

DR VOLWILER That is a reasonable explanation.

#### CLINICAL DIAGNOSIS

Gastric ulcer, benign

#### DR VOLWILER'S DIAGNOSIS

Carcinoma of stomach

#### ANATOMICAL DIAGNOSIS

*Benign peptic ulcer*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN This patient was operated on through the chest by Dr Carroll Miller. He did a subtotal gastrectomy and found, 4 cm from the esophageal orifice on the lesser curvature, a large ulcer that had eroded into the pancreas. On gross examination the ulcer looked benign, although it was surrounded by a good deal of inflammatory reaction. Microscopically, sections confirmed the benign character of the lesion. It was an active ulcer, with a red-staining, fibrinoid base similar to that seen in active peptic ulcers.

DR VOLWILER Do we know anything about the incidence of recurrence of benign peptic ulcer with that sort of anastomosis? The top part of the stomach is removed, and the major acid-bearing portion and antrum are left in.



DR WELCH That is an interesting question, but we do not know anything about it yet. The antral mucosa remains, and there may be an increased tendency toward recurrence.

DR CASTLEMAN Still, you would not want to advise total gastrectomy at the first operation?

DR WELCH No.

DR SCHATZKI Have there been recurrences in cases in which that procedure has been done?

DR WELCH No recurrences have been observed to date, although the number of patients is small and the time interval short.

## CASE 33272

### PRESENTATION OF CASE

An eighteen-month-old boy entered the hospital because of edema of the face and lower extremities.

The child had been perfectly well until about three months before admission, when the first signs of an illness characterized by restlessness, irritability and a low-grade fever had developed. He slept and ate poorly and ran a continuous fever, the temperature never exceeding 101°F. After a few days, periorbital swelling appeared. The administration of tincture of digitalis for three days was sufficient to cause the edema to subside, but it recurred ten days after the drug had been withdrawn. Another course of digitalis was followed by a long remission during which the patient was kept inactive in bed. He occasionally refused a meal, but ate well at other times and did not appear ill. During this interval a heart murmur was heard for the first time. About three weeks before entry the child had suffered a brief attack of sore throat. Two weeks later he again appeared ill, with rapid panting respiration and slight cyanosis. On the day preceding admission edema of the lower extremities began to develop.

Birth had occurred at term after a normal gestation period. No complications accompanied the delivery or the neonatal period. The birth weight was 6 pounds, 11½ ounces. Mental and physical development proceeded normally until the present illness. The heart sounds were said to have been normal a year before the present illness. There were no siblings, and no familial diseases were reported.

Physical examination disclosed a child lying flat in bed and breathing rapidly at a rate of 36 per minute. The skin was dusky and cyanotic, the neck veins pulsated in the sitting position. Slight pitting edema extended over the ankles and lower portions of the legs. The chest was asymmetrical, bulging over the precordium. The heart was greatly enlarged to both the left and the right. The sounds had a pounding quality. The rhythm was regular. A loud, rather harsh systolic murmur audible all over the precordium radiated to the axilla and was heard posteriorly on both sides. A rolling mid-

diastolic murmur was heard best beneath the nipple and in the axilla. Both lung fields were clear. The liver edge extended 6 cm below the rib margin. No clubbing of the fingers was noted. Femoral pulsations were present. The patient weighed 20 pounds and was 30 inches tall.

The temperature was 98°F, the pulse 106, and the respirations 150. The blood pressure was 90 systolic, 60 diastolic.

Examination of the blood revealed a red-cell count of 4,650,000, with a hemoglobin of 10.9 gm, and a white-cell count of 19,200 that subsequently fell gradually to 8700. The urine gave a + to ++ test for albumin, and the sediment contained 0 to 4 red cells and 4 or 5 white cells per high-power field. In several 7-foot films of the chest, the heart shadow was greatly enlarged, the transverse diameter being 12.5 cm compared to an internal thoracic diameter of 15.5 cm., the contours were smoothly ovoid. No calcification was visible within the heart area. On fluoroscopy the pulsations were normal. The ribs were horizontal, and in addition, on the right side there was an anomaly of the fourth, fifth and sixth ribs. The lower-lung fields were almost completely obscured except at the bases laterally, where they were clear. The upper-lung fields were hazy. The pulmonary vascular markings were accentuated. No transposition of the great vessels could be detected. An electrocardiogram demonstrated sinoauricular tachycardia, and low T waves in Leads 1, 2 and 3, but the axis and PR interval were normal.

Treatment consisted of digitalis and restriction of fluids. A maintenance dose of 20 mg of digitalis daily sufficed to control the cardiac failure. By the tenth hospital day, the patient's general appearance was good. He was no longer dyspneic, and the edema had absorbed. Repetition of the chest films failed to demonstrate any marked change in the heart size. Another electrocardiogram recorded a drop in the rate to 100 per minute and a rise in the voltage of the T waves.

On the tenth day, mild coryza developed without fever. It lasted three days and then cleared spontaneously. A throat culture grew out a few colonies of Type 17 pneumococci, but subsequent ones were negative. Four blood samples were cultured in the course of a week. One was sterile in both flasks, nonhemolytic streptococci, *Staphylococcus aureus* and diphtheroids, respectively, were recovered from one flask in each of the other three cultures. The erythrocyte sedimentation rate (Westergren) at the end of the bout of coryza was 2 mm per hour, and on the twenty-fifth day it reached 16.5 mm per hour. The child was discharged home in the care of his physician on the twenty-sixth day.

About a year after discharge, the patient reported that the p... , saying fa... without dyspnea... was ta... of digitalis six d... - club

fingers had developed. The liver was palpable but nontender and not definitely enlarged. The heart remained extremely large.

At the age of three and a half years the patient weighed 31 pounds and was slightly over 38 inches tall. His condition was still fair, but a thrill had developed over the xiphoid process.

At the age of four he developed pneumonia, which cleared rapidly with penicillin, but from then on he had a bothersome cough and began to be decompensated. Edema first appeared in the extremities and then spread upward. Two months after the occurrence of the pneumonia, edema, ascites and dyspnea were severe. The patient died soon afterward.

### DIFFERENTIAL DIAGNOSIS

**DR RALPH A. ROSS:** This case of recurrent cardiac decompensation started at the age of fifteen months and progressed, with remissions and recurrences, for nearly three years. The patient had been well up to the onset of the illness. He responded well to digitalis until the agonal period. The fact that physical development, which was said to have been normal for an eighteen-month-old infant, was at the lower limits for the age group may or may not be of significance. At the age of three and a half years the patient was well within the normal limits, so that if he was below par at admission to the hospital he made up for slow growth before he died.

On physical examination there were the classic signs of decompensation, — dyspnea, cyanosis, increased venous pressure, pulmonary congestion, hepatomegaly and edema, — as well as periorbital edema, which is unusual. The progressive signs of valvular damage are clear from the record, starting with a precordial systolic murmur before the first admission and then a definite mid-diastolic murmur over the mitral area, finally, a thrill developed before death.

The x-ray films showed general cardiac enlargement. May we see them? There were good pulsations on fluoroscopic examination, which seem to rule out a large collection of fluid.

**DR TOUFIC KALIL:** These are the rib anomalies. The heart is enlarged in all diameters, and the carina is widened behind the heart. The left main bronchus is raised considerably, which indicates some degree of enlargement of the left auricle, as well as of the ventricles.

**DR ROSS:** The electrocardiograms are not particularly helpful, indicating on the second tracing that some benefit, which could be determined from the clinical picture, had occurred. There was at no time any indication of polycythemia. There was a transient leukocytosis at the onset of the hospital stay. The urinary findings are probably explained best on the basis of cardiac decompensation. Certainly, the onset of periorbital edema, the acute decompensation, the enlargement of the heart and the

response to digitalis can be explained by myocarditis associated with glomerulonephritis, but the lack of further urinary findings and the subsequent course of the disease are against that diagnosis. There are other, more esoteric conditions that should be considered — von Gierke's disease, the glycogen-storage abnormality that occurs sometimes predominantly in the heart without much involvement of the rest of the body, clinically seems unlikely in a child who lived for four and a half years and grew relatively normally. We have no indication that there was any acetone in the urine or that the adrenalin test was done. I think that that diagnosis is unlikely. Interstitial myocarditis, described by Fiedler,<sup>1</sup> is a possibility if there is no other explanation for the enlarged heart. I simply bring it up as a thought. I do not know how we can go farther than that with it. Recently, at the Children's Hospital a case was diagnosed pathologically in a patient who had lived for a year without obvious cardiac symptoms, entered the hospital with what were thought to be pulmonary symptoms and died with a diagnosis of interstitial myocarditis as the only cause for the symptoms.

In favor of congenital heart disease is the presence of other anomalies, particularly those of the ribs. Congenital anomalies tend to be multiple. The bulging of the thorax noted three months after the onset of symptoms could have been due to acquired heart disease in a child of that age. How can we explain the progressive signs on the basis of congenital heart disease? The patient could have had bacterial endocarditis. The blood cultures in the hospital were negative. The long course after admission makes a diagnosis of subacute bacterial endocarditis untenable. An acute terminal bacterial endocarditis may, of course, have developed after the pneumonia. This leads me to the final possibility — acquired rheumatic heart disease. So far as rheumatic fever is concerned, no family history was noted, and the child was quite young, the disease, however, is occasionally seen at this age. The febrile episode before the onset of cardiac symptoms, the exacerbation two weeks after the respiratory infection, the failure of an exacerbation after pharyngitis apparently due to pneumococcus, the adequate growth of the child and the progressive development of murmurs seem to me to support the diagnosis of acquired rheumatic heart disease. Against this diagnosis is the response to digitalis. Usually, in children, cardiac decompensation associated with rheumatic heart disease is on the basis of acute infection, and digitalis rarely works so effectively as it apparently did in this case. The normal sedimentation rate can be disregarded because the child was probably in some degree of cardiac failure. Thus, I am left with the diagnosis of rheumatic heart disease and myocarditis, with mitral stenosis.

**DR GERTRUD C. REYERSBACH:** We were as puzzled as Dr. Ross, and he has mentioned the

points that made us doubt whether the child had rheumatic fever. We finally decided on rheumatic fever as a working diagnosis, but we were never quite convinced. The subsequent course does not bear it out. The child never had episodes of rheumatic fever according to what happened later. He developed a thrill over the xiphoid area, which is not consistent with mitral stenosis.

DR PAUL D WHITE I think that the murmurs observed in the hospital can be explained on the basis of enlargement of the heart alone without valvular disease necessarily. Frequently, during the early stages of rheumatic heart disease, perhaps in the first few years of a history of rheumatic fever, even mitral diastolic murmurs can be explained wholly by dilatation of the heart, without valvular deformity. Just what the thrill meant I do not know, but I do not recall that I found a thrill when I examined this patient at the time of admission. I should want to feel such a thrill before committing myself. It does look as if an infectious process were more probable than a congenital defect, because there had been fever and leukocytosis and no clear-cut characteristics of congenital anomalies — there was no clubbing of the fingers, for example. The cyanosis noted at first cleared up. It was not a constant cyanosis?

DR REYERSBACH No.

DR WHITE The electrocardiogram was normal, which is important from the standpoint of many congenital defects of the heart in which it would be abnormal. It could be normal in various infections, as for example acute rheumatic fever, despite the age, and that is to my mind the likeliest. Years ago I looked up the cardiac cases of infants, less than two years of age, with acute endocarditis at the Infants' Hospital in Boston, and as I recall there were a number of cases of bacterial infection but I do not remember finding any cases of rheumatic valvular involvement or rheumatic heart disease. Certainly, the diagnosis of pericarditis alone is not acceptable. Digitalis may help congestive failure in the presence of active rheumatic fever if the patient is treated at a favorable time — when the active infection has begun to subside.

#### CLINICAL DIAGNOSIS

Rheumatic heart disease, with mitral insufficiency

DR ROSS'S DIAGNOSES

Rheumatic fever

Rheumatic heart disease, with mitral involvement

#### ANATOMICAL DIAGNOSES

*Healed endocarditis, type undetermined, of mitral and tricuspid valves and ventricular endocardium*

Hypertrophy of heart

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY When a case is dubious on clinical grounds it often remains dubious on anatomic grounds. I was puzzled by this case too.

The flaps of the mitral valve were thickened and interadherent, and the chordae were shortened. There was a similar, although slighter, change in the tricuspid valve. The aortic and pulmonary valves were perfectly normal. Besides these valvular changes there were two unusual features. One was hypertrophy. The heart was four times the normal size for a child of this age. The hypertrophy was rather generalized in all chambers. There was also a marked degree of thickening in the ventricular endocardium. This appeared in patches in all four chambers and was almost diffuse in the left ventricle. We have a considerable number of sections from the heart, and microscopically they all show extreme thickening of the endocardium extending along the thebesian vessels into the myocardium but otherwise no trace of myocardial scarring, nowhere in the heart could we find anything that suggested an active rheumatic lesion. Sections of the valve showed simply a marked thickening of the connective tissue and some mucinous degeneration, but no inflammatory infiltration whatsoever, this does not suggest the picture of rheumatic endocarditis.

I am reminded of the case of another child that we had at these conferences a number of years ago, in which the clinical picture had been one of uncontrollable tachycardia of many months' duration. In that case the valves were negative, but there was the same thickening of the endocardium that this child showed. It was even more marked than in the case under discussion. It is rather flying in the face of Providence, when there is mitral stenosis and tricuspid involvement, to say that this was not rheumatic endocarditis, and yet I have genuine doubt that it was. If it was not rheumatic endocarditis, I do not know what it was.

DR WHITE Could bacterial endocarditis have produced this picture?

DR MALLORY I do not see how it could have. Endocardial fibrosis was marked and a characteristic feature of the whole process in the heart. I should not expect that with bacterial endocarditis, which is sharply limited to the leaflets or endocardium close to the valves. I should also not expect it to be spread diffusely on the ventricular endocardium.

DR WHITE Has Dr Bland any suggestions?

DR EDWARD F BLAND I have never seen anything like the patient that Dr Mallory has referred to, who died of a cerebral embolism. There was no embolus involved in the case under discussion. It does not sound like rheumatic heart disease clinically.

DR MALLORY We have seen few children die of rheumatic heart disease in the absence of active rheumatic infection.

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## A SUBACUTE AND MALIGNANT FORM OF EPIDEMIC HEPATITIS

INFECTION hepatitis and homologous serum jaundice are generally regarded as relatively mild diseases that are associated with a low mortality rate—about 0.2 per cent. Recovery is usually complete. Cases do occur, however, in which these infections are followed by a long-standing disability with a variety of symptoms referable to the liver or nervous system, or both.<sup>1-3</sup>

Lucke<sup>4</sup> described the pathological findings in the livers of 14 cases observed in the Army after apparent recovery from epidemic hepatitis. The livers had become available for examination as a result of fatal accidents or unrelated diseases from one to

fourteen months after the attack of hepatitis. From the study of these livers, Lucke concluded that complete restoration of the hepatic parenchyma usually occurs in nonfatal cases of hepatitis. Regeneration is usually complete provided that the destruction is acute and the injury is not continued and provided also that the destructive changes involve only the hepatic cells and not the framework or vessels, all this generally holds true in epidemic hepatitis. Lucke could find no evidence of permanent damage to the hepatic parenchyma.

Variants from the usual form of hepatitis have been observed in the recent pandemic of hepatitis. Attention has been called in these columns to the fulminant type described by Lucké and Mallory,<sup>5</sup> in which death from acute hepatitis occurred within a period of less than ten days after the onset of symptoms. In Denmark another malignant form of hepatitis has been observed in recent years. In the cases that were observed there, death occurred several months after the onset of acute hepatitis. Reports of cases of this type are now available from hospitals in Copenhagen. One by Jersild appears elsewhere in this issue of the *Journal*, and another by Alsted<sup>6</sup> has recently been published. The malignant hepatitis observed in Denmark has occurred predominantly in women over forty-five years of age and has a fatality rate of about 50 per cent. The duration of illness is usually from four to nine months, but both more acute and more protracted cases have been observed. Clinically the cases are characterized by jaundice, recurrent attacks of pain associated with fever and evidence of portal obstruction—that is, edema and ascites. There is persistent evidence of impaired liver function. The pathological findings are largely limited to the liver, in which there is widespread destruction of liver tissue and, in the relatively chronic cases, replacement by connective tissue.

The etiology of this form of hepatitis remains obscure. On epidemiologic grounds it is believed that this type has a different cause than that of the usual cases of epidemic hepatitis and that it is different from homologous serum jaundice. Indeed, the possibility is considered that it may not even be an infectious disease, although no alternative causes have been suggested. Similarly, no effective therapy

has been found other than the usual dietary and supportive regimes that are used in cases of hepatitis

The possibility that some special dietary or hormonal factors have altered the course of epidemic hepatitis in Denmark has been considered, but no evidence to support such a hypothesis has been offered. Interestingly enough, reports of similar cases from other European countries have not yet appeared, although it is possible that they have been encountered. Likewise, no such cases have as yet been recorded in large numbers in this country.

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DE SENECTUTE

THE lines "Gather ye rosebuds while ye may" and so forth, familiar to all of us, are still appropriate in these days of longer life but of accelerated living. They are, moreover, by one who knew his old age, Robert Herrick having put eighty-two summers behind him even in the seventeenth century, when the average span of man's life was well under forty years.

Not only has the duration of life nearly doubled since the over-ripe Herrick wrote his somewhat amorous lyrics, as a result, the average age of the populations of civilized countries has likewise steadily increased. The old, like the poor, will definitely be with us, and we must look to the better care of the aging, if they are to enjoy the fullness of their years. We must put more emphasis on the last of Shakespeare's seven periods of existence if we are to try and save the "lean and slipper'd pantaloons" from

second childishness, and mere oblivion,  
Sans teeth, sans eyes, sans taste, sans everything

This interest in the problems of the old is fortunately quickening, here and abroad, to the point where geriatrics, caring for the tapering end of the

life line, has become as serious a specialty as has pediatrics for its beginning. It is wise to bear in mind that the sunset of man's life may have as vivid colors as its dawn, and he is much more conscious of it.

As Dr. Roger I. Lee\* has pointed out, we have, by our care of the young, permitted many more people to become elderly without doing much to make that increase in years any happier or even more endurable. One of our tasks is to make these added years, for which most of us hope and which most of us dread, more pleasant ones to anticipate and to attain.

The declining years of life should have their own activities and their own compensations and their own type of oversight. They require certain dietary limitations, as of fats and roughage, and certain dietary reinforcements, as of vitamins and even digestants. Indeed, some of the proprietary firms are already promoting pap for the aged as well as pap for the young.

Age has its dignity, too often lost, let it also have its comfort, too often lacking. Let our second childhood at least share the consideration given our first. The enthusiastic lines of Rabbi Ben Ezra,

Grow old along with me!  
The best is yet to be,  
The last of life, for which the first is made,

particularly appropriate for a geriatric slogan, hold a promise that is still not always fulfilled but offers a target at which to shoot.

\*Lee, R. I. Geriatrics: medical care of elderly. *New Eng. J. Med.* 230: 190-193, 1944.

MASSACHUSETTS MEDICAL SOCIETY  
A M A ANALYSIS OF POSTWAR  
QUESTIONNAIRE

Discharged medical officers, according to an authorization from the American Medical Association, are entitled to one copy each of the "Analysis of the Postwar Questionnaire," which may be obtained from Frank G. Dickinson, Director, Bureau of Medical Economic Research, American Medical Association, 535 North Dearborn Street, Chicago 10.

This questionnaire was sent in November and December, 1946, to the 50,681 medical officers who were discharged prior to December 31, and sought opinions on the handling of medical matters during the war, with suggestions for improvement. Usable questionnaires returned totaled 26,018.

JOSEPH GARLAND, Secretary

## BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## DISTRIBUTION OF TOXIN-ANTITOXIN DISCONTINUED

The Public Health Council of the Commonwealth of Massachusetts voted on May 13 to discontinue the distribution of toxin-antitoxin mixture on June 30. This action is in accord with the recommendations of the National Institute of Health and of authorities on diphtheria immunization who have for some time past been unanimous in the opinion that toxin-antitoxin mixtures should be entirely replaced by diphtheria toxoid for diphtheria immunization.

For the information of those who have not before used diphtheria toxoid in immunizing adolescents and adults, the following points should be emphasized.

## Recommendations

All children between six months and high school age should be immunized with diphtheria toxoid. The Schick test need not be performed on them before immunization since the majority of children of this age group are susceptible to diphtheria.

The Schick test should be performed on all persons of high-school age or over who are exposed to diphtheria or who are likely to come in contact with it. Interpretation of the test indicates subsequent procedure as follows:

- Schick positive control negative susceptible. Administer diphtheria toxoid with precautions as described below.
- Schick positive control positive but smaller: immunity status uncertain. Such subjects are sensitive to the proteins of the diphtheria bacillus and may exhibit marked reactions to toxoid. Since they are few in number they may be re-Schicked two weeks later this test being read at seven days. A negative test indicates that the subject possesses latent immunity awakened by the first test and therefore need not be immunized. If the test is positive, administer diphtheria toxoid with caution in small divided doses (see below).
- Schick and control show approximately equal reactions immune but sensitive to diphtheria bacillus proteins ("pseudoreaction"). No immunization indicated.
- Schick negative, control negative immune. No immunization indicated.

## Dosage

For children three doses of 0.5, 1.0 and 1.0 cc. respectively given at intervals of three or four weeks, are advised. Fewer doses or administration at shorter intervals may fail to produce immunity. Injections should be made subcutaneously after preparing the skin at the site of injection with tincture of iodine and alcohol. Do not inject more than 1.0 cc. Discard remaining contents of used vials at end of clinic session.

The standard dosage schedule given above may cause moderate or occasional marked reactions in older children and adults. For this reason the first dose in such patients should be 0.1 cc. If no marked reaction follows, subsequent doses should be 0.5, 1.0 and 1.0 cc. respectively. If a marked reaction occurs, the dosage can be adjusted in accordance with the severity

of the reaction, and the interval between doses shortened provided a total of 2.5 cc. is administered.

## Precautions

Local and even general reactions are exceptional in younger children, older children and adults are more liable to have severe local and general reactions so that toxoid should be given them only as described above. The reactions consist of varying degrees of redness, induration and swelling at the site of injection, sometimes accompanied by malaise, fever and headache which usually clear up within two days.

## Duration of Immunity Reimmunization

Immunity of the level indicated by a negative Schick test develops in 90 to 95 per cent of children within three months after the administration of the last dose of diphtheria toxoid and may be expected to persist for at least several years. Follow up Schick tests six months after immunization will detect those who fail to respond to one immunizing course. Such persons should be given another series of inoculations.

It is recommended that children entering school who were immunized in infancy be given a stimulating dose of not over 0.5 cc. of toxoid. This is of particular importance in communities where the low incidence of diphtheria makes it advisable to compensate for the consequent lack of latent immunization.

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR MAY, 1947

## RESUME

DISEASE	MAY 1947	MAY 1946	SEVEN YEAR MEDIAN
Chancroid	0	4	14
Chicken pox	2598	2248	1276
Diphtheria	38	21	14
Dog bite	1253	1421	1335
Dysentery bacillary	5	3	13
German measles	107	1469	640
Gonorrhea	273	340	340
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	0	3*
Malaria	10	69	12
Measles	1783	11494	4108
Meningitis meningococcal	3	2	16
Meningitis, Pfeiffer bacillus	8	7	7
Meningitis, pneumococcal	1	4	6†
Meningitis staphylococcal	0	0	0†
Meningitis streptococcal	0	1	2†
Meningitis other forms	3	1	1†
Meningitis, undetermined	7	1	3†
Mumps	1095	922	1459
Pneumonia, lobar	172	117	232
Poliomyelitis	0	1	1
Salmonellosis	14	1	6
Scarlet fever	440	851	1120
Syphilis	279	439	439
Tuberculosis, pulmonary	256	342	306
Tuberculosis, other forms	26	23	23
Typhoid fever	1	2	2
Undulant fever	8	6	6
Whooping cough	495	573	670
*Three-year median			
†Five-year median			

## COMMENT

The diseases above the seven year median are chicken pox, diphtheria, Pfeiffer bacillus meningitis, salmonellosis and undulant fever.

Although below the prevalence for April diphtheria was still above the level in May 1946, and the seven year median. The decrease was probably largely due to the usual seasonal decline.

The increase in salmonellosis is not explained by an out break since more than one case was reported from only three communities and all those reported only two cases.

The diseases below the seven year median are bacillary dysentery, German measles, measles, meningococcal meningitis, mumps, poliomyelitis, scarlet fever and whooping cough.

This is the second consecutive month in which no cases of poliomyelitis were reported.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston 13, Brookline 1, Chelsea 10, Easthampton 2, Everett 1, Framingham 1, Hinsdale 1, Lynn 1, Manon 3, Medford 1, Revere 1, Somerville 1, Wakefield 1, Worcester, 1 total, 38.

Dysentery amebic was reported from Lawrence 1 total 1.

Dysentery, bacillary, was reported from Worcester (State Hospital), 5, total, 5

Encephalitis, infectious, was reported from Taunton, 1, total, 1

Malaria was reported from Berkley, 1, Boston, 2, Haverhill, 1, Lynn, 1, Middleton, 1, Springfield, 1, Taunton, 1, Winchendon, 1, Worcester, 1, total, 10

Meningitis, meningococcal, was reported from Boston, 1, Fitchburg, 1, Lynn, 1, total, 3

Meningitis, Pfeiffer-bacillus, was reported from Boston, 2, Cambridge, 1, Chicopee, 1, Fitchburg, 1, Lowell, 1, Medford, 1, Northampton, 1, total, 8

Meningitis, pneumococcal, was reported from Cambridge, 1, total, 1

Meningitis, other forms, was reported from Boston, 2, Sudbury, 1, total, 3

Meningitis, undetermined, was reported from Brockton, 1, Cambridge, 1, Great Barrington, 1, Holbrook, 1, Northampton, 1, Springfield, 1, Wrentham, 1, total, 7

Salmonellosis was reported from Belmont, 1, Beverly, 1, Boston, 1, Grafton, 1, Lowell, 1, Quincy, 1, Revere, 1, Somerville, 2, Waltham, 2, Winchendon, 2, Worcester, 1, total, 14

Septic sore throat was reported from Boston, 7, Grafton, 1, Merrimac, 1, Taunton, 1, total, 10

Trichinosis was reported from Boston, 2, total, 2

Tularemia was reported from Springfield, 1, total, 1

Typhoid fever was reported from Quincy, 1, total, 1

Undulant fever was reported from Ashburnham, 1, Foxboro, 1, Ludlow, 1, Newton, 1, Paxton, 1, Weymouth, 1, Worcester, 2, total, 8

#### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	July 7	Paul W. Hugenberger
Gardner (Worcester Subclinic)	July 8	John W. O'Meara
Pittsfield	July 9	Frank A. Slowick
Brockton	July 10	George W. Van Gorder
Worcester	July 18	John W. O'Meara
Hyannis	July 24	Paul L. Norton
Fall River	July 28	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments

## REPORT OF MEETING

### MASSACHUSETTS CENTRAL HEALTH COUNCIL

The annual meeting of the Massachusetts Central Health Council was held on May 1. The topic for discussion concerned local health councils, and the work of several of the more active local health councils was described.

Speaking for the Boston Health League, Miss Margaret Tracy stressed the importance for Boston of continuing the school-lunch program, as conducted in the Boston public schools by the director for school lunches, Miss Upham. The Health League has an active Committee on School Hygiene under the chairmanship of Dr. Charles H. Bradford. This committee is now studying problems relating to lunch-room services in the public schools of Boston. Another committee of the Boston Health League, under Mr. Horace Morison, is working on the question of reorientation of the work of the League in order that its usefulness may be increased.

The Health Committee of the Needham Community Council has been functioning for only one year, but Mrs. Francis K. Dermody was able to report that this committee has already been instrumental in the establishment of a much needed dental clinic.

Dr. Henry Godfrey, chairman of the Division of Hygiene of the Newton Community Council, reported that his committee has been successful in promoting x-ray examinations for tuberculosis among factory workers, has prepared health posters, is planning first-aid services for factories, is engaged

in cancer instruction for the public and is active in the field of nutrition.

Reporting for the Health Division of the Wellesley Community Council, Prof. Curtis M. Hilliard spoke of its service in an advisory capacity to men and women who have served in the armed forces, he also stressed its unique type of mental health program, and its co-operation with the Board of Health in the field of dental work and accident prevention. Each problem has been approached systematically. The first step is to study the matter, and the second to confer with all agencies involved and to formulate a program, the final step is to promote the program through interpretation to the public. Professor Hilliard summed up by saying: "It is hard to see, now that we have a community council how we could have gotten along without one."

Dr. James O. Walls, city health officer of Worcester, spoke for the four-year-old Health Division of the Worcester Community Council. Its groups cover the family and child, park and recreation, health, nutrition, crippled and handicapped and miscellaneous. The nutrition group brought the various nationalities together and secured better relations among them. The health division, by pushing, has doubled the budget for child guidance. The health group has done much to promote harmony and co-ordination of health programs in Worcester.

Mrs. Eleanor S. Washburn, director of the recently organized Massachusetts Community Organization Service, spoke briefly of its aims. She said that its purposes are to provide state-wide advisory services to communities concerning the basic requirements for sound, well rounded health, welfare, educational and recreational programs, to work for better co-ordination of the state-wide agencies, both public and privately supported, to promote local community planning co-ordinated with state planning, to give or secure technical assistance with community surveys and to provide an information service concerning social and health resources. Mrs. Washburn believes that her organization can assist the Central Health Council in its program of strengthening the organization of local health councils in many localities in which health councils have not yet been formed.

In opening the discussion, Dr. Elmer S. Bagnall, president of the Massachusetts Medical Society, stressed the great potential value of local health councils and expressed his interest in this phase of the program.

Mr. A. J. Strawson pointed out the importance of careful planning of the program in order that the interest of the participating may be fruitful and sustained.

Initial indifference and apathy, said Professor Hilliard, are inevitable, but they can be overcome by enthusiasm.

Dr. Hugh R. Leavell said that health councils should be organized on a voluntary basis and that adequate attention should be given to financing them.

At the business meeting of the Council the resignations of the president, Dr. George C. Shattuck, and of the vice-president, Dr. Channing Frothingham, were presented. The officers elected for the ensuing year were Dr. Hugh R. Leavell, president, Dr. David L. Belding, vice-president and Mr. Arthur J. Strawson, secretary-treasurer.

## NOTICES

### ANNOUNCEMENTS

Dr. Irving E. Goldberg, whose office is at 270 Commonwealth Avenue, Boston, announces that he has recently become a member of the Boston Anesthesia Service.

Dr. Sydney Grace announces the removal of his office from the practice of obstetrics and gynecology to 475 Commonwealth Avenue (Lister Building), Boston.

Dr. Otto Kant announces the opening of an office for the practice of neuropsychiatry at 19 Bay State Road, Boston. He is also retaining his Worcester office.

Dr. John C. Tate, who has returned from military service, announces the reopening of an office at 83 State Street, Springfield, for the practice of surgery.

(Notices continued on page xiii)

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## TOTAL GASTRECTOMY

With Particular Reference to Closed (Aseptic) Esophagojejunostomy

REGINALD H. SMITHWICK, M.D.\*

BOSTON

A DISCUSSION of carcinoma of the stomach should not fail to emphasize three points: the earliest symptoms of the disease are often mild and insidious and may consist of nothing more than indigestion, loss of appetite or easy fatigability, there is a great need for earlier diagnosis and operation if the survival rates are to be improved, and carcinoma of the stomach is responsible for more deaths per year than cancer of any other organ and for approximately 30 per cent of the total annual cancer mortality.

Many cases — 50 per cent in Ogilvie's<sup>1</sup> series — were obviously hopeless when first seen. Twenty per cent are found to be inoperable by pentoneoscopy or exploratory laparotomy. In a recent discussion of this problem Anglem<sup>2</sup> found 70 per cent of 188 cases to be inoperable for one reason or another. In a high percentage of resectable cases metastases have already occurred to the regional lymph nodes, thus significantly reducing the statistical chances for long survival or cure. In other cases direct extension of the growth to adjacent organs makes resection extremely difficult, inadvisable or impossible. In some cases the involvement of the stomach is so extensive that nothing less than a total gastrectomy can be considered.

This operation was first attempted by Conner<sup>3</sup> in 1883. The first survival was reported by Schlatter<sup>4</sup> in 1897. Since that time many articles have appeared in the literature. When Finney and Rienhoff<sup>5</sup> discussed the matter in 1927, they were able to collect from the literature and their own 5 cases, a total of 67 patients who had been subjected to total gastrectomy. The operative mortality approximated 50 per cent, in 58 per cent of cases the cause of death was peritonitis. In 1933 Roeder<sup>6</sup> reported 3 cases, and so far as he could determine the total

number of gastrectomies recorded at that time was 88. The operative mortality was 50 per cent. He likewise emphasized the importance of peritonitis as a cause of death. In 1938 Allen<sup>7</sup> reported 15 cases with 7 deaths — a mortality of 47 per cent. In their monograph on carcinoma of the stomach published in 1942, Walters, Gray and Priestley<sup>8</sup> placed the operative mortality between 40 and 50 per cent and found peritonitis to be the cause of death in 55.6 per cent of cases. In 1944 Lahey and Marshall<sup>9</sup> observed an operative mortality of 33 per cent, peritonitis being the cause of death in 58 per cent of fatal cases. These representative reports from the literature serve to emphasize two points: the over-all operative mortality following total gastrectomy has been high, and the principal cause of death has been peritonitis. In spite of this, a survey of the current literature reveals a notable reduction in operative mortality. In a series of 103 cases of total gastrectomy reported since 1942 and including the cases referred to below, there were only 15 operative deaths.<sup>10-17</sup>

It is quite impossible to point to a single factor that is entirely responsible for this favorable trend. Better preoperative preparation and postoperative care are important. The advent of chemotherapy has without doubt exerted a favorable influence. Improvement in the technic of anesthesia — particularly in the administration of intratracheal ether and continuous spinal and procaine block — should also be mentioned. It has seemed to me, however, both from a survey of the literature and from my own few experiences, that the noteworthy reduction in operative mortality following total gastrectomy is due principally to improvements in surgical technic.

Many points about the technic of total gastrectomy have been emphasized. First of all are those related to an adequate operation for carcinoma, such as removal of regional lymph nodes and the great omentum. Other matters are stressed by

\*Presented at the annual meeting of the New England Surgical Society, Worcester, October 5, 1946.

<sup>1</sup>Professor of surgery, Boston University School of Medicine; surgeon-in-chief, Massachusetts Memorial Hospitals; member, Board of Consultation, Massachusetts General Hospital.



some and not by others, such as mobilization of the left lobe of the liver, removal of the spleen and the question of whether the jejunal loop should be brought up in front of or behind the colon, whether some plastic procedure on the jejunal loops should be performed to make a substitute pouch for the stomach and whether some particular form of anesthesia should always be used. To my mind, these considerations are significant but not of primary importance. The need for an entero-enterostomy has been insisted on by some and minimized by others, the majority appear to favor this method. Routine jejunostomy for postoperative

and Graham employ an additional layer of interrupted suture material between the esophagus and the jejunum prior to the placement of the inner continuous suture line. All emphasize the need for precaution against contamination by means of suction within the esophagus or externally and of careful walling off of the general peritoneal cavity. *It is at this particular point in the performance of total gastrectomy that most of the seeds of peritonitis are sown.* This may result in death solely from contamination at the time of operation. Fatal peritonitis may be due to subsequent separation and leakage from the anastomosis, which may be

TABLE 1 *Technic and Results of Total Gastrectomy in 10 Cases*

CASE NO	TYPE OF ANASTOMOSIS	TYPE OF ESOPHAGO JEJUNOSTOMY	POSTOPERATIVE COMPLICATIONS	RESULT
1	End to side	Open	Peritonitis	Operative death
2	End to side	Open	Peritonitis and empyema	Operative death
3	End to side	Open	Excessive febrile response, local peritonitis?	Patient living and well 10½ years after operation
4	Allen	Closed (aseptic)	Spontaneous tension pneumothorax	Patient dead of disease 8 months after operation
5	Lahey	Closed (aseptic)	None	Patient living and well 5 years and 2 months after operation
6	Allen	Closed (aseptic)	None	Patient dead of disease 2 years and 1 month after operation
7*	Graham	Closed (aseptic)	None	Patient living and well 3 years and 2 months after operation
8	Graham	Closed (aseptic)	None	Patient dead of disease 3 months after operation
9	Graham	Closed (aseptic)	None	Patient dead of disease 8 months after operation
10	Graham	Closed (aseptic)	None	Patient living with recurrence 1 year and 1 month after operation

\*This patient had a large ulcer situated on the greater curvature of the fundus of the stomach that was thought to be malignant but proved to be benign. All the other patients had carcinoma.

feeding, which has been suggested, may be regarded as optional — useful in some cases, but not essential in all. The incision of choice varies, but by and large, one placed to the left of the midline retracting the rectus muscle laterally and extending well up alongside the ensiform seems satisfactory. The costal cartilages can be divided if necessary. Care should be taken not to open the pleura. Of great value is the technic of esophagojejunal anastomosis. A major portion of the reduction in current operative mortality appears to be due to improvements in this particular step of the operation.

Many excellent articles have been written about total gastrectomy. Several authors — particularly Allen,<sup>7, 18</sup> Lahey,<sup>19</sup> Lahey and Marshall<sup>9, 20</sup> and Graham<sup>21</sup> — have stressed the technic of esophagojejunal anastomosis. Their articles have had a favorable effect on current operative mortality. There is one point in common — namely, the use of an outer layer of sutures between the jejunum and the diaphragm. This is generally a layer of interrupted, nonabsorbable suture material. Allen combines this with an inner continuous suture between the esophagus and the jejunum. Lahey

the result of impaired circulation, undue tension or delayed healing from contamination at the time of anastomosis.

My experiences are quite representative of those in the literature in general (Table 1). In brief, there were 2 operative deaths in 10 cases. In 3 cases an open anastomosis was performed. Both deaths occurred in this group and were due to peritonitis. End-to-side anastomoses were made between the esophagus and the jejunum, an outer layer of interrupted nonabsorbable suture material and an inner layer of continuous fine catgut being employed. The jejunum was not suspended to the diaphragm. One patient is alive and well ten and a half years after operation. In the second group of 7 cases, a similar suture technic was used. There were two variations, however, an outer layer of interrupted nonabsorbable suture material between the jejunum and the diaphragm was used according to the methods of Allen, Lahey or Graham. In addition, all anastomoses were of a closed or what might be called an "aseptic" variety. These were performed by a technic that has been found to be

safe and applicable to all other portions of the gastrointestinal tract.<sup>22</sup>

My impression is that a closed technic of esophagojejunal anastomosis is a practical and useful adjunct to methods previously described in that it retains their most essential feature — namely, an outer suspensory suture line between the jejunum and the diaphragm — and at the same time further safeguards against the hazard of peritonitis due to contamination during open suture methods. There were no operative deaths and no evidence of peritonitis or wound infection in the 7 cases in which this procedure was employed. Its use in the various steps of total gastrectomy, including enteroenterostomy and closure of the duodenal stump, is illustrated in Figures 1, 2 and 3.

Of the 7 patients who survived total gastrectomy by the closed or aseptic technic, 2 are living and well three years and two months and five years and two months, respectively, following operation. The former was thought to have carcinoma both from the preoperative data and from the gross appearance at operation. Microscopically, however, the lesion proved to be a large, benign ulcer on the greater curvature of the fundus. In the latter case, the tumor was extensive, involving the pancreas and the transverse mesocolon. It was fixed and at first seemed inoperable. After a large portion of the transverse mesocolon, including a segment of the middle colic artery, had been resected, the spleen mobilized, and the tail and body of the pancreas resected immediately to the left of the superior mesenteric vessels, the lesion was found to be operable. It was not necessary to resect the transverse colon, the collateral circulation being adequate.

Thus, there were five-year survivals in 2 of the 9 cases of carcinoma, the second being that of the patient mentioned above who is living and well ten and a half years after operation. The lesions in both cases were large and palpable prior to operation and so extensive that nothing less than total excision could be performed. The regional lymph nodes were not involved. The preoperative and postoperative x-ray films and the microscopical characteristics of the tumors are shown in Figures 4, 5, 6 and 7.

Previous to 1946 the longest reported survival after total gastrectomy for carcinoma was that of Zikoff's<sup>23</sup> patient, who lived for four years and eight months after an operation performed in 1911. Recently, Lahey<sup>10</sup> reported a patient living and well five years and four months after operation. He also recorded 2 patients living and well, respectively, seven years and one month following total gastrectomy for lymphosarcoma and eight years and seven months after total resection for leiomyosarcoma. These lesions are rare by comparison with carcinoma, and the long-range outlook is apparently better. At present, therefore, 3 patients who have lived for five years or more following total gastrec-

tomy for carcinoma are on record. The data are insufficient to permit the construction of survival curves following total gastrectomy, but some idea of the statistical chances of being alive from one

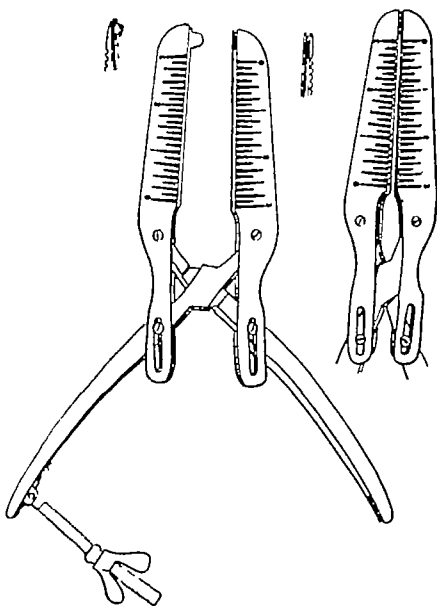


FIGURE 1

*This thin-bladed clamp is placed on the end or side of the portion of intestine to be closed or anastomosed. The blades approximate in a parallel fashion, thus ensuring secure holding and equally distributed pressure on all portions of the segment included within it. A thumb-screw driver permits controlled closure of the blades to the point of moderate crushing of the tissues. The width of the crushed tissue is about 1.5 mm. The bowel is divided distal to the clamp with a cautery, leaving a thin segment of tissue above the surface of the blade. This is cauterized slowly until it is black and well charred. This charred tissue is also about 1.5 mm. in thickness. A running suture is then placed in the charred tissue, constituting the first layer in the event that an end is to be turned in. If an anastomosis is to be performed, a basting suture is placed in the charred tissue instead. The grooves on the surface of the clamp are placed 3.0 mm. apart, and the running or basting suture is placed in these. The surface of the clamp is marked in inches to facilitate the selection of comparable portions of tissue for anastomosis. After either the running or basting suture is placed the clamp is removed. This technic provides complete hemostasis. The width of the turned-in tissue is narrow — about 3.0 mm. The turned-in tissue, which is completely deslialized, separates in a few days. Anastomoses always open spontaneously when the basting sutures are withdrawn. There is no residual diaphragm to cause stenosis either immediately or later.*

to ten years after operation is indicated in Table 2. Because of the marked reduction that has recently occurred in operative mortality following total gastrectomy, it seems proper to consider extending its use somewhat, particularly in cases involving

the body of the stomach in which a subtotal resection can be done but in which the margin of safety

ably have had total gastrectomies in the past had the mortality of the procedure not been prohibitive.

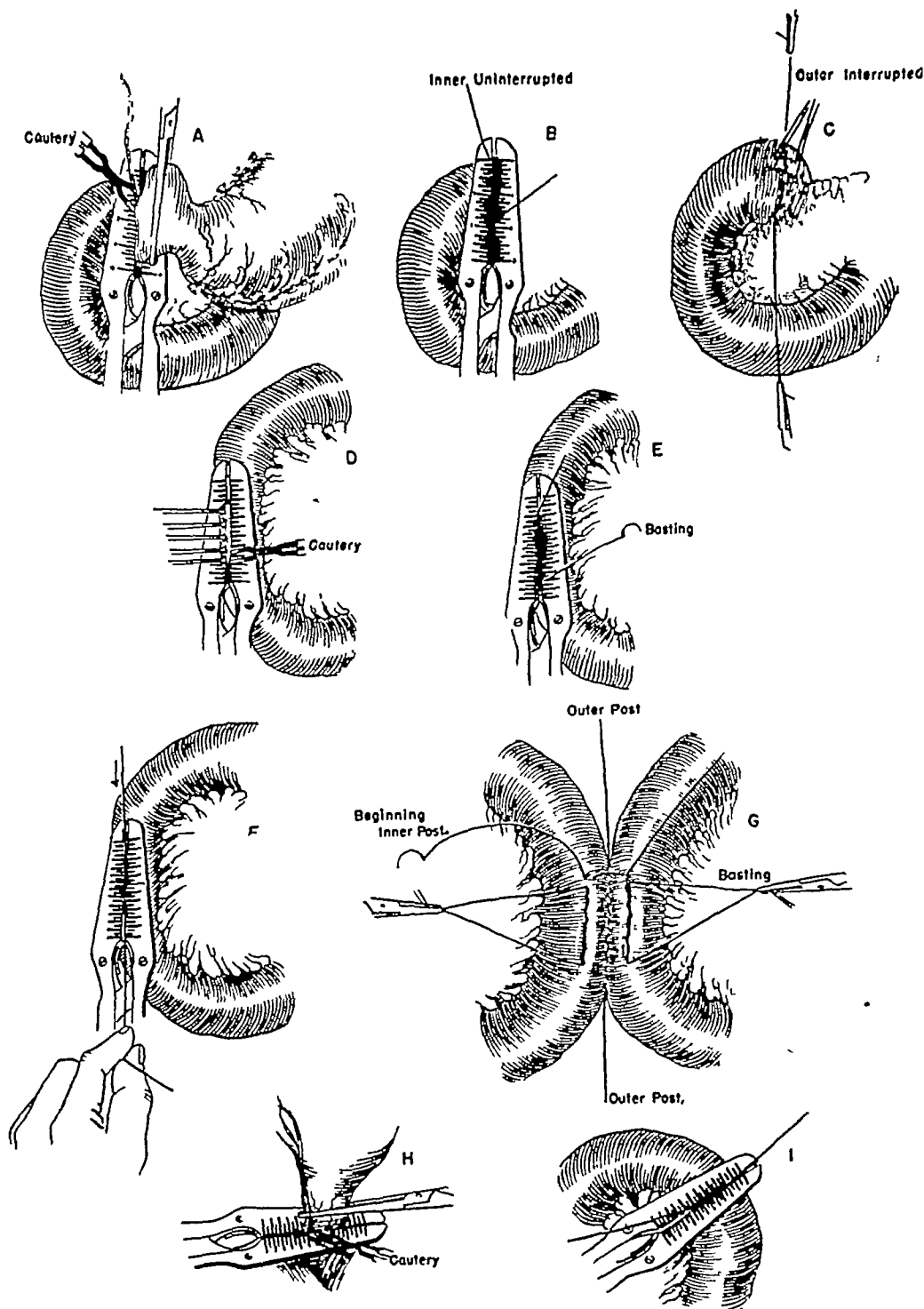


FIGURE 2

In the operation of total gastrectomy, it is necessary to turn in the duodenal stump (A, B, C) to perform an enteroenterostomy between the jejunal loops (D, E, F, G), and an end-to-side anastomosis between the esophagus and the jejunum (H, I). The use of this clamp in performing these various steps is illustrated. A running suture in the cholel, as well as a second serosal layer of sutures either interrupted or continuous, absorbable or nonabsorbable, the latter being covered by a tab of omentum, makes an adequate closure of the duodenal stump. An additional suture line in the serosa can be used if necessary. Two layers of fine continuous catgut are used in the performance of an enteroenterostomy.

above the gross limits of the disease is questionable. A significant number of such patients would prob-

The extension of the indications for total gastrectomy has already been suggested by Morton.<sup>16</sup>

Two late complications are of interest among the 10 cases presented in Table 1. One patient (Case 3)

of material, usually bile. This complication occurred with gradually increasing frequency and was particularly troublesome at night. At times, she eructated

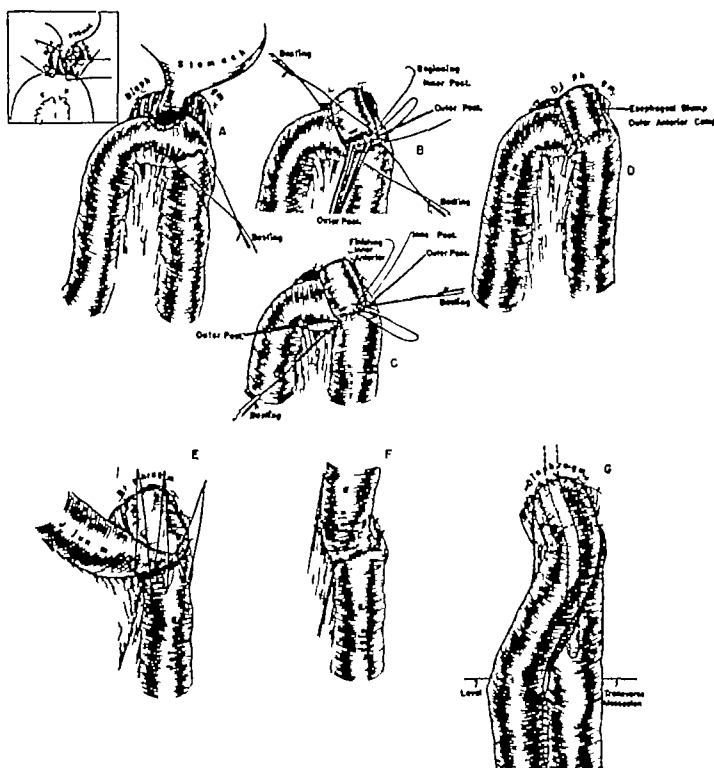


FIGURE 3

In the performance of an end-to-side anastomosis between the esophagus and the jejunum, an outer layer of interrupted nonabsorbable suture material is used to suspend the jejunum to the diaphragm. A second similar layer is used between the esophagus and the jejunum. The third or inner layer is between the esophagus and the jejunum and is of fine, continuous catgut. The various steps of esophago-jejunojejunostomy are shown utilizing the Graham technique modified to the extent that the anastomosis is of the closed or aseptic variety. The jejunal loop is suspended to the diaphragm posterior to the esophagus with four or five interrupted nonabsorbable sutures in such fashion that the proximal loop is more redundant than the distal (A). A basting suture has previously been placed transversely in the distal jejunal loop (A). A posterior layer of interrupted nonabsorbable sutures is then placed between the esophagus and the jejunum (B). The esophagus is then divided and the end closed with a basting suture. An inner, continuous catgut suture is placed between the esophagus and the jejunum, cutting the previous sutures one at a time as each bite of the continuous layer is taken (B, C). This layer is then completed anteriorly, at which point the basting sutures are withdrawn. The outer interrupted anterior layer of sutures is then completed (D). As a final step the proximal redundant jejunal loop is wrapped over the anastomosis and attached to the diaphragm superiorly and to the distal jejunal loop laterally and inferiorly. Interrupted nonabsorbable suture material is used for this layer. In this technique an entero-enterostomy is obligatory because the proximal jejunal loop is more or less obstructed (E, F, G).

did well for about six months after operation, eating small meals frequently. She then began to have episodes of sudden regurgitation of a large amount

as much as 500 cc of bile-stained material with little warning. Approximately a year after the original procedure, a second operation was per-

formed. The proximal jejunal loop was found to be markedly dilated and hypertrophied by comparison with the distal loop. The enteroenterostomy was found to have closed itself almost completely except for a minute opening between the two loops. A new large enteroenterostomy was made, and there

longer necessary. The patients are out of bed the day after operation and are able to leave the hospital in fourteen days or less, at which time they are tolerating a six-meal soft-solid diet. At first, they eat small quantities at a time, but in a year or so they do much better as the jejunum gradually

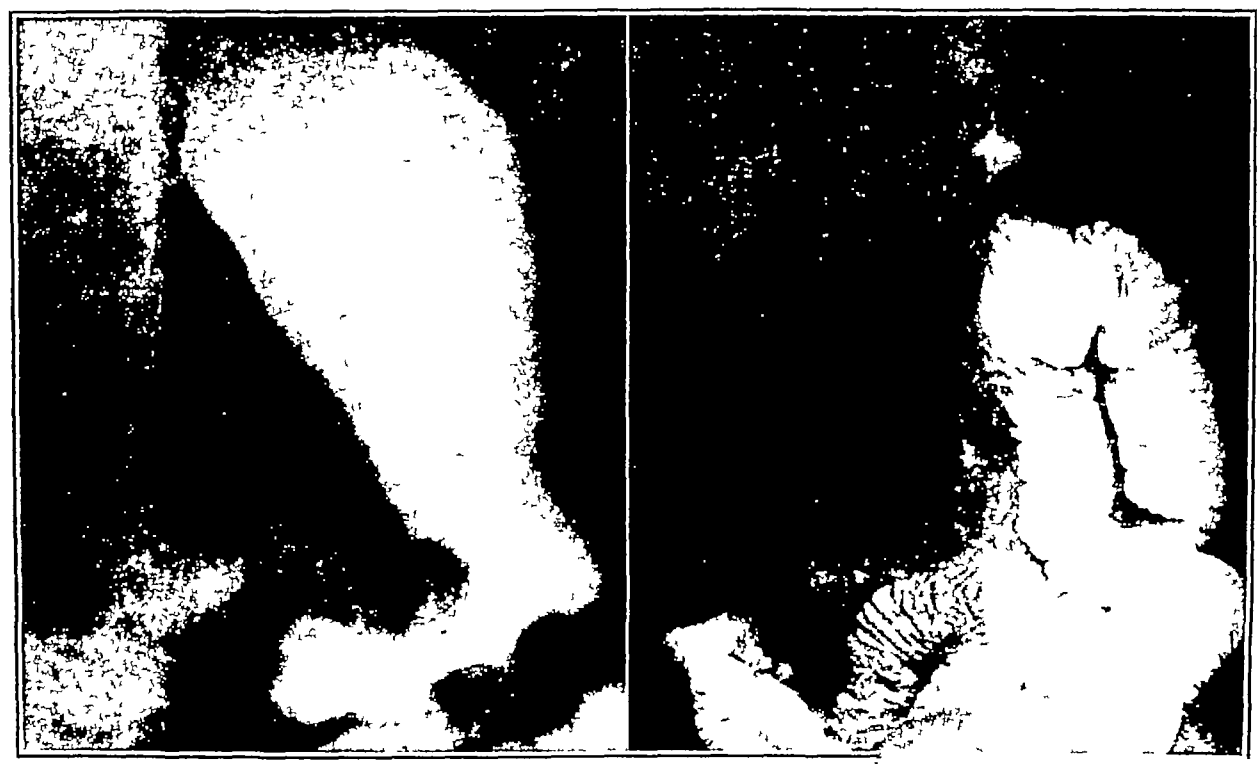


FIGURE 4 Case 3

The x-ray film on the left was taken preoperatively. There was a large annular growth pylorus distally and to within a centimeter of the esophagus proximally. The film on after operation. There is a well functioning anastomosis between the esophagus and jejunal loops.

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has been no recurrence of the difficulty during the past nine and a half years. The patient in Case 10 had an extremely useful immediate postoperative convalescence.

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TABLE 2 Percentage of Survivals after Total Gastrectomy

AUTHOR	No OF CASES	SURVIVALS					
		1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	10
		%	%	%	%	%	%
Lahey	57	60	30	21	—	—	—
Smithwick	9	44	33	22	22	22	11

last few cases, as we have become more confident about the anastomosis, we have removed the nasal tube at the completion of the operation and have permitted the patients to take fluid in small quantities by mouth at the end of twenty-four hours. Water in sips up to about 15 cc each hour is given at first and increased each day as tolerated, other liquids containing protein and carbohydrate in particular being added, so that at the end of four or five days supplementary parenteral fluid is no

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made approximately two and a half months after the original operation. This was done by a trans-thoracic approach. There was no gross evidence of carcinoma in the specimen, which consisted of several centimeters of esophagus and jejunum. Malignant cells, however, were revealed by the microscope. About three weeks later, a further segment of duodenum was removed. Again, gross evidence of carcinoma was lacking, but the disease was apparent microscopically. The patient is now living a year and one month after the original operation, but is failing rapidly. There is a large neoplastic mass in the epigastrium, and he is having further difficulty in swallowing. A recent biopsy from the esophagus revealed evidence of carcinoma in the region of the anastomosis. This case serves to emphasize the need for removing a safe margin of normal tissue beyond the gross limits of the disease. If the lower end of the esophagus is known to be involved, a transthoracic approach should be used. Sweet<sup>28</sup> reported a series of total gastrectomies performed by this approach. In 2 cases the lower end of the esophagus was not involved. In 1 case a combined thoracoabdominal approach was used. There is no reason why the advantages of both the abdominal and the thoracic approaches cannot be utilized if necessary.

The remote effects of total gastrectomy on protein, carbohydrate, fat metabolism and intestinal motility and hematopoiesis are of interest. Few

Rekers, Pack and Rhoads<sup>4</sup> studied 3 patients for three to fourteen months after total gastrectomy



FIGURE 5 Case 3

*This is a photomicrograph of a section of the tumor which was a Grade II adenocarcinoma. The regional lymph nodes were not involved.*

Disturbances in fat metabolism were found in all, and of protein metabolism in 1. All had anemia of varying degree of the normochromic, normocytic

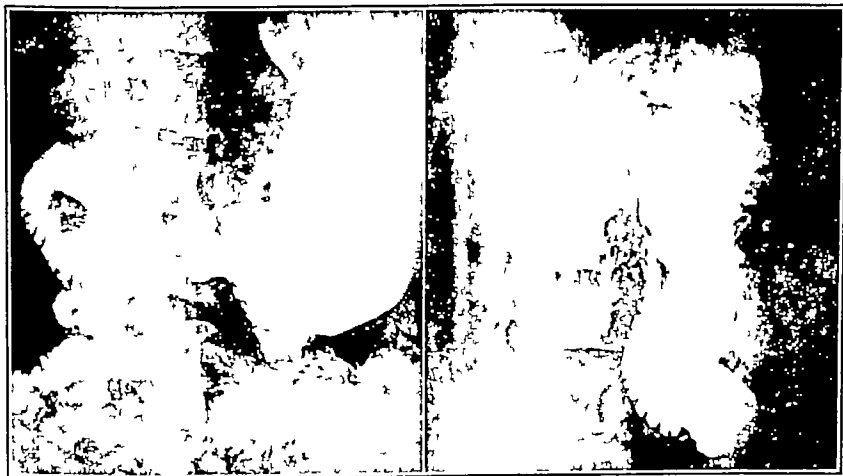


FIGURE 6 Case 5

*The x ray film on the left was taken preoperatively. There was an extensive tumor reaching from the pylorus to the esophagus, with involvement of the pancreas and transverse mesocolon. The film of the right was taken five years and two months after operation. There is marked dilatation of the jejunal loops.*

studies of this sort are on record long after total removal of the stomach

type. No evidence of macrocytic anemia was found. Farris, Ransom and Collier<sup>11</sup> observed 4

formed. The proximal jejunal loop was found to be markedly dilated and hypertrophied by comparison with the distal loop. The enteroenterostomy was found to have closed itself almost completely except for a minute opening between the two loops. A new large enteroenterostomy was made, and there

longer necessary. The patients are out of bed the day after operation and are able to leave the hospital in fourteen days or less, at which time they are tolerating a six-meal soft-solid diet. At first, they eat small quantities at a time, but in a year or so they do much better as the jejunum gradually

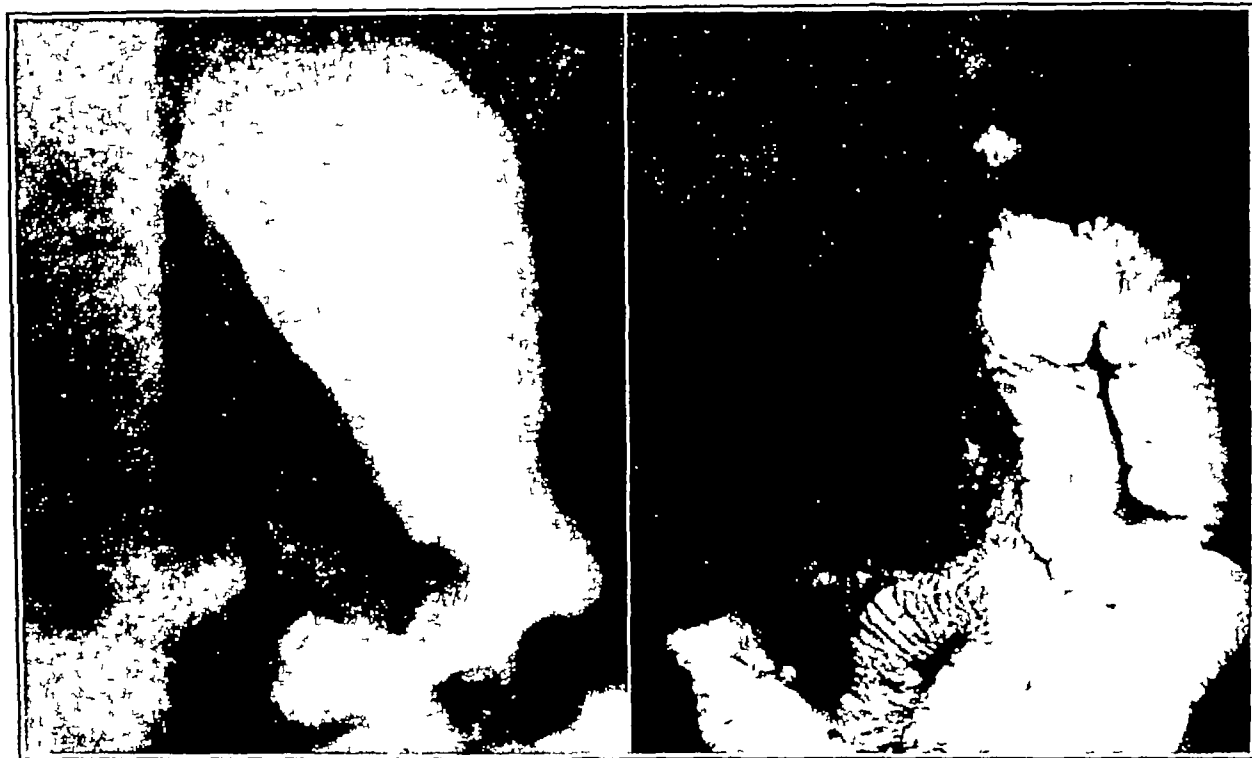


FIGURE 4 Case 3

The x-ray film on the left was taken preoperatively. There was a large annular growth in the antral region that extended to the pylorus distally and to within a centimeter of the esophagus proximally. The film on the right was taken ten and a half years after operation. There is a well functioning anastomosis between the esophagus and jejunum, with moderate dilatation of the jejunal loops.

has been no recurrence of the difficulty during the past nine and a half years.

The patient in Case 10 had an extremely uneventful immediate postoperative convalescence. In the

TABLE 2 Percentage of Survivals after Total Gastrectomy

AUTHOR	NO OF CASES	SURVIVALS					
		1 YR.	2 YR.	3 YR.	4 YR.	5 YR.	10 YR.
		%	%	%	%	%	%
Lahey	57	60	30	21	—	—	—
Smithwick	9	44	33	22	22	22	11

last few cases, as we have become more confident about the anastomosis, we have removed the nasal tube at the completion of the operation and have permitted the patients to take fluid in small quantities by mouth at the end of twenty-four hours. Water in sips up to about 15 cc. each hour is given at first and increased each day as tolerated, other liquids containing protein and carbohydrate in particular being added, so that at the end of four or five days supplementary parenteral fluids are no

dilates. In the course of years the loops become large. In Case 10, however, the patient began to experience difficulty in swallowing a few weeks after discharge. This progressed rapidly to the point of almost total obstruction in six additional weeks. This suggested the probability of residual cancer, since benign strictures following esophagojejunostomy usually do not progress so rapidly and are generally readily managed by dilatation. This patient did not respond to dilatation in the usual fashion, and a review of the specimen removed at operation revealed malignant cells extending to the limit of the resected esophagus. It also revealed that extension had occurred into the duodenal segment as well. There was no gross evidence of this at the time of operation. We thought we were well beyond the limits of the growth at both ends of the specimen. An x-ray film taken two weeks after operation showed a well functioning anastomosis and should be compared with a second taken four weeks later, which indicated almost total obstruction (Fig. 8). The esophagojejunal anastomosis was resected, and a new anastomosis was

## SUMMARY

The need for earlier diagnosis and earlier treatment of carcinoma of the stomach is emphasized. The frequency of this lesion and its importance as a cause of death are commented on.

A survey of the literature indicates a noteworthy recent decrease in operative mortality following total gastrectomy. Because of this, it seems proper to utilize this operation somewhat more frequently, particularly in cases in which a lesser procedure may jeopardize the chance for cure because of an inadequate margin of safety beyond the gross limits of disease.

Although the lower current operative mortality for total gastrectomy is undoubtedly due to a combination of factors, it is believed that improved surgical technic is one of the most important.

A closed (aseptic) method for esophagojejunostomy is described. This technic of anastomosis may further reduce the operative mortality by minimizing the hazard of peritonitis due to local contamination. The procedure has in other respects been as satisfactory as open methods of suture and has been found useful in all portions of the gastrointestinal tract.

Late complications, survival rates and remote effects of operation are commented on.

Two cases are reported in which the patients are living and well five years and two months and ten and a half years respectively following total gastrectomy for carcinoma. The latter appears to be the longest recorded survival following total gastrectomy for carcinoma.

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## DISCUSSION

DR. FRANK H. LAHEY (Boston): I think that we should all report our results with total gastrectomy because no one has dealt with this subject without being uncertain of the wisdom of the procedure. One of the early things that I said to our group is that when we have done enough total gastrectomies we must be sure that they are worth while, because so much of the stomach is involved in these cases of carcinoma, leiomyosarcoma or lymphosarcoma in which total gastrectomy is carried out that obviously the prospects of cure are slight.

We must then determine the prospects of prolongation of life and whether or not the operations are worth while. We have now done total gastrectomy in 92 cases over a period of years and Dr. Frances H. Smith, of the Clinic, has sent to *Surgery, Gynecology and Obstetrics* a good follow up study of 87 of these cases. As a result of this study it can be anticipated that 50 per cent of patients will survive for twelve months, 39 per cent for eighteen months, 30 per cent for twenty four months and 21 per cent for three years or more.

We have had a patient who had a total gastrectomy for leiomyosarcoma and who is alive and well nine years after operation, another, with lymphosarcoma, is alive and well seven years and eight months after operation. Still another is alive six years, and a fourth with carcinoma is alive and well six years after operation.

It is of interest to note the improvement in mortality. Our mortality for the entire series is 29 per cent. In the last 43 cases the mortality has been reduced to 16 per cent, and I do not believe that we have had a death in total gastrectomy in the last three years.

We no longer fear leakage. I think that our early mortality was largely the result of poor selection and selection, it seems to me is the consideration that must be urged on surgeons who are beginning their experience with total gastrectomy.

There are a number of things that one should do. I have published an article on operability with the abdomen open, in carcinoma of the stomach. We should be certain that there are not gravity metastases in the pelvis and particularly certain after direct inspection that there are not extensions in the root of the mesentery as demonstrated with the transverse colon turned up. One should be positive that there are not nodular chains running up the side of the esophagus through the diaphragm. These are often discovered only after the total gastrectomy is quite well along. Nothing I know of is so distressing as to have completed all the steps of a total gastrectomy except the anastomosis to the jejunum and to become aware of the fact that the lesion extends up beside the esophagus and is inoperable.

One of the things that should interest everyone is the blood picture after the operation. Dr. Smith has reviewed these cases and has found that 79 per cent of patients have red cell counts of 4,000,000 or higher. It is true that some of them must have assistance but it shows that they can maintain good blood pictures. Forty per cent had hemoglobin values of 13 gm.

In total gastrectomy there are any number of practical technical steps that we have learned from this experience. We have no fear of the open anastomoses. After the spleen has been removed, the left lobe of the liver has been mobilized and the vagi have been severed the esophagus can be pulled down a considerable distance and the anastomosis can be done relatively close to the abdominal wall.

For any of you who may do this operation, Dr. Marshall has devised what I think is one of the best steps toward making the operation easier — that is, the introduction of the posterior interrupted silk stitches, first leaving long loops with the esophagus turned up so that the interrupted stitches



are put in with long loops on the jejunum before the jejunum is opened. The jejunum is then opened well down in the field, and the loops must be pulled up and approximated. It is difficult to approximate the jejunum on the back of the esophagus unless it is done in this way. Total gastrectomy is technically feasible and is not too difficult an operation. Enteroenterostomy is desirable. In the last half of our cases all have had enteroenterostomies, because there is an irritating effect from the presence of bile regurgitating into the lower end of the esophagus, producing an esophagitis.

It is true that the linitis plastica type of carcinoma has a low grade of malignancy, because otherwise it is inconceivable that many of these patients in whom the entire stomach is replaced by carcinoma can have survived for a number of years. The linitis plastica type of carcinoma of the stomach must be a different lesion from the local carcinomas, which are often hopeless and recur quickly.

For that reason, I urge that everyone become familiar with this not too difficult operative procedure, particularly in the type of carcinoma that uses its energy in intramural infiltration rather than local ulceration and early metastatic involvement of neighboring structures.

DR CLAUDE C KELLY (Hartford, Connecticut) I have followed a patient for seven years after total gastrectomy. The patient has had a good deal of trouble in the last year. He did not report regularly for follow-up study. He was sent to a medical specialist, who found pernicious anemia. The patient was treated for that condition and is now working every day.

DR SMITHWICK (closing) Dr Kelly's seven-year cure following total gastrectomy for carcinoma is, of course, unusual, and his comments concerning the development of a primary type of anemia in this patient are of considerable interest, particularly the fact that the anemia has responded well to treatment.

The 3 patients in the series that I have reported today who are alive three, five and ten years after total gastrectomy

are at present being studied carefully from a metabolic point of view, with particular reference to the question of anemia.

Strangely enough there have been few reports of the primary type of anemia following total gastrectomy. Moynihan described a patient in detail who lived for three years and seven months following total gastrectomy for carcinoma and developed a severe anemia that was apparently fatal. Autopsy failed to reveal any evidence of carcinoma. The data, however, did not indicate with certainty the type of anemia. Most comments in the literature regarding anemia following total gastrectomy indicate that it has almost invariably been of a secondary variety. Most of these patients, however, were studied fairly soon after operation, and it is wholly possible that if more patients survive for longer periods there will be a higher incidence of primary anemia. In any event it apparently can be fairly readily managed by specific therapy so that it does not detract from an active and useful existence.

Other changes following total gastrectomy are of interest. There may be a disturbance in fat metabolism and a rather marked alteration in intestinal motility. There is considerable delay in the passage of barium from the jejunum to the large bowel, presumably owing to the lack of vagal innervation.

The marked reduction in operative mortality following total gastrectomy seems to make it proper to consider the use of this operation more frequently than in the past, particularly in patients with carcinoma of the body of the stomach that can be resected, leaving an inadequate margin of safety above the growth. I am certain that I, as well as many others, have avoided total gastrectomy in certain cases of this sort because of the high mortality. I believe that the time has come when one may properly be more radical under such circumstances.

## THE EFFECT OF LARGE DOSAGES OF IRRADIATION ON GASTRIC ACIDITY

IRVING B. BRICK, M.D.\*

BOSTON

**I**N PREVIOUS articles cases of gastric ulceration and the complications of hemorrhage and perforation incident to abdominal irradiation have been reported.<sup>1,2</sup> In 6 cases, 4 of which are illustrated in Table 1, it was necessary to perform gastric resection. In these cases, as well as in many others of a similar type, treatment was given at the Radiation Therapy Section, Walter Reed General Hospital, for retroperitoneal metastatic disease or as a prophylaxis therefor in cases of testicular tumor. A 1,000,000-volt machine was used, and with the technics devised by Lieutenant Colonel Milton Friedman the dosage delivered to the stomach could be determined accurately. It was considered necessary to use a large x-ray dosage because of the radioresistance of some of these tumors and because of the metastatic involvement already present in some cases.

None of the patients had had previous gastrointestinal symptomatology or disease. Thus, coincidentally, the effects of irradiation on normal stomachs could be noted.

\*Resident, Fifth and Sixth Medical Services (Boston University), Boston City Hospital, formerly, chief Gastrointestinal Section, Walter Reed General Hospital, Washington, D. C.

For some time since Bruegel<sup>3</sup> reported the production of a temporary achlorhydria with radiation therapy, the use of x-ray therapy in peptic ulcer has held the attention of many workers. In studies on both human beings and animals, with great variations in technics and dosages, the consensus appears to be that there is a variable depression or suppression of gastric acidity. Palmer and Templeton,<sup>4</sup> who present the most complete data, as well as a review of the previous work on this problem, are representatives of the school of thought that considers acid gastric juice to play an important role in the pathogenesis and healing of peptic ulcer. Achievement of neutralization or inhibition of acid secretion is therefore regarded as a highly desirable therapeutic goal. Before describing their results, the authors emphasize the potential dangers of radiation therapy, calling attention to reported cases of radiation injury to the small intestine and liver and also to the stomach in cases of carcinoma. No mention is made, however, of radiation injury to the normal stomach.

Palmer and Templeton treated 100 cases of peptic ulcer involving the stomach, duodenum and jejunum

with large dosages of radiation therapy, which they considered safe. A 200-kilovolt machine was used with 15-by-15-cm portals anteriorly and posteriorly over the upper part of the stomach and with occasional positional check by fluoroscopy. Dosages varying from 1100 to 3600 r (measured in air) were employed. The authors concluded that there was definite gastric secretory depression, whose extent and duration were extremely variable and unre-

tors included 1000 kilovolts, 3 milliamperes, a filter of 3 mm tungsten and a focal skin distance of 70 or 100 cm, 88 to 40r, respectively, being delivered per minute. With the size of the portals used, 10 by 10 cm in most cases, the dosage of radiation was delivered to the antrum of the stomach, rather than to the upper part. In previous studies it was shown that the effects both radiographically and pathologically are confined mainly to the antral

TABLE 1 Data in Cases of Gastric Ulcer with Complications Requiring Partial Gastrectomy

CASE NO	CLINICAL DIAGNOSIS	X-RAY DOSAGE r	DURATION OF THERAPY days	GASTRIC ANALYSIS WITH HISTAMINE* mEq/100 ml	INTERVAL AFTER IRRADIATION days	REMARKS
1	Teratocarcinoma of right testicle with metastases to retroperitoneal lymph nodes	6456	3	0-65-115 100-65	69	Partial gastric resection 95 days after irradiation revealed perforation of an ulcer 3 cm in diameter on posterior wall; hematocrits also observed
2	Sarcoma of right testicle with metastases to retroperitoneal lymph nodes	6105	49	11-21-49 50-38 0-0-45 6-46	152 180	Partial gastric resection 203 days after irradiation revealed perforation of ulcer 3 cm in diameter on posterior wall
3	Teratoma, mixed type, of right testicle with no metastases to retroperitoneal lymph nodes	4800	53	0-0-0 0-0 0-0 35- 5- 0 0-20-26 18- 4	57 71 222	Partial gastric resection 223 days after irradiation revealed ulcer 2.5 cm in diameter near pylorus with walled-off abscess between greater curvature and transverse colon; bleeding from ulcer resulted in profound anemia
4	Carcinoma of left testis	5096	54	0-0-77 55-5 0-0-40 1-25	97 159	Partial gastric resection 189 days after irradiation revealed triangular ulcer 1.8 x 1.7 cm, in pyloric ring posterior to lesser curvature

\*Fractional analysis with 0.5 cc. of histamine; first number represents fasting specimen, ults of free hydrochloric acid and other numbers specimens taken at fifteen minute intervals

dictable. A few toxic reactions were noted, including localized hepatic necrosis, diarrhea and anemia. No conclusions were drawn concerning the effect of radiation on peptic ulcer since the patients were given concurrent standard Sippy acid neutralization management. Histamine achlorhydria was observed after treatment in 35 of the 88 cases, the known duration of achlorhydria varying from a few days to a few months. The degree of depression of gastric acidity was not found to be related to initial acidity, sex, age, height, body weight, depth dose or dose of radiation. The high degree of individual variation is impressive. Palmer and Templeton soundly conclude that "the final effect of irradiation, not only on gastric secretion and the course of ulcer, but also on the normal tissue within the field of radiation, remains still to be determined."

#### MATERIAL AND METHOD

In the results presented below, there were marked differences in the clinical material from that of Palmer and Templeton. Our patients had normal stomachs and coincidentally received irradiation in the treatment of metastatic disease or in its prophylaxis. Unfortunately, values of gastric acidity were not obtained prior to radiation, and the data represent chronic, rather than acute, effects. The amount of irradiation given is in terms of tumor dose delivered at the level of the eleventh dorsal vertebra with a 1,000,000-volt machine. The physical fac-

tor and pyloric regions.<sup>1,2</sup> Fractional gastric analysis with 0.5 cc. of histamine was performed in all cases.

#### RESULTS

Table 1 presents 4 cases in which partial gastric resection was performed because of the complications of gastric ulceration. The radiation doses were high, being over 6000 r in 2 cases and 4800 and 5096 r in the others. Perforation of the stomach was observed at operation in 3 cases, and yet the values of gastric acidity varied from low normal in 1 case to high in another, whereas the third was normal. Hemorrhage occurred in 2 cases, in 1 the values of gastric acidity were high, whereas in the other the values were low. The patient who received the smallest radiation dose (Case 3) had the most marked depression of gastric acidity. Fifty-seven days after completion of radiation, there was histamine achlorhydria. A hundred and sixty-five days later and one day prior to partial gastric resection, the values of acidity were still low, but at operation the patient had a large antral ulcer with subacute perforation and peritonitis. Certainly, the attainment of normal to low values of gastric acidity in this case was of no aid in preventing the serious complications of ulcer. Although the immediate effect on acidity of radiation in these cases was not obtained, it appears that no definite pattern of depression or stimulation is present after two months following completion of radiation.

Table 2 presents 5 cases in which the diagnosis of ulceration of the antral portion of the stomach was made by x-ray study or gastroscopy, or both. In these cases, at this writing, no complications have occurred, and the patients have improved symptomatically and by objective study. Again, there was no definite pattern of effect. In all the cases except

vertebra, was suspected of having caused radiation injury to the stomach. In all the other cases, the radiation dose was well above 4000 r. It might be argued that the ulcer was merely a coincidental occurrence, but the time of onset in relation to radiation therapy, the atypicality of symptoms, the antral location of the ulcer, the spasticity of the

TABLE 2 *Data in Cases of Gastric Ulcer with Improvement*

CASE No	CLINICAL DIAGNOSIS	X-RAY DOSAGE r	DURATION OF THERAPY days	GASTRIC ANALYSIS WITH HISTAMINE* units	INTERVAL AFTER IRRADIATION days	REMARKS
5	Embryonal carcinoma of right testis, with no metastases to retroperitoneal lymph nodes	5280	63	0-70-0-0-80 28-88-172-145-110 0-48-66-32-30	80 128 66	Ulcer of antrum, 4 cm in diameter, visible by x-ray study and gastroscopy, patient improving on medical regime
6	Embryonal carcinoma of right testis, with no metastases to retroperitoneal lymph nodes	5304	54	0-36-0-0-0 10-61-30-28-18 0-33-37-10-20	148 173 205	Ulcer disclosed on x-ray examination and gastroscopy marked improvement on medical regime
7	Seminoma of right testis, with metastases to retroperitoneal lymph nodes	5350	62	0-10-20-0-8	471	Moderate changes in antrum, with ulcer niche, observed on x-ray examination
8	Hypernephroma of right kidney, with metastases to retroperitoneal lymph nodes, nephrectomy performed	5376	54	46-42-40-96-30	186	Patient asymptomatic, with no demonstrable ulcers, at time of gastric analysis, several ulcers demonstrated in stomach by x-ray study and gastroscopy 1 mo after completion of treatment
9	Seminoma of left testis	2424	30	0-34-16-21-22	59	X-ray study and gastroscopy disclosed ulcer, which disappeared after treatment, no previous gastrointestinal disease

\*Fractional analysis with 0.5 cc of histamine: first number represents fasting specimen in units of free hydrochloric acid, and other numbers specimens taken at fifteen-minute intervals.

one the dose was above 5000 r. The exception is worthy of detailed consideration.

**CASE 9.** A 31-year-old man had a seminoma of the left testicle removed on March 20, 1946. There was no history of gastrointestinal symptoms or disease. The patient received prophylactic radiation from April 17 to May 17, to the following levels: suprapubic, 2370 r, fourth lumbar, 2880 r, and eleventh dorsal, 2424 r. During treatment he had nausea for only 2 days. The patient felt well until 19 days after completion of radiation when he experienced pain in the epigastrium. The pain was described as a dull ache, with occasional periods of sharp burning lasting about 1 hour. There was no definite relation of the pain to meals, nor was relief afforded by food or soda. Attacks of pain lasting 1 hour were noted in the early morning. There was little nausea or vomiting and no hematemesis or melena. Vomiting was induced by the patient during an attack without relief.

Physical examination was negative except for pigmented brown areas over the radiation portals on the anterior abdomen. A gastrointestinal film on June 29 showed some spasticity of the antrum with a normal mucosal pattern. No organic lesion was noted in the esophagus, stomach or duodenum. Because of continuing symptoms, gastroscopy was performed on July 23, and an ulcer, 6 mm in diameter, was found on the greater curvature of the antrum just distal to the anterior end of the angulus. The ulcer was deep and clean, and its base was gray. There was no exudate or bleeding, and the margins of the ulcer showed no inflammatory reaction. A repeat x-ray film on July 27 showed an ulcer and a spastic antrum.

The patient was placed on a strict ulcer regime with alleviation of symptoms. At this writing, the patient has only occasional epigastric discomfort, which is of little consequence. Gastroscopy performed twice since the initial examination at intervals of 2 weeks showed slow healing of the ulcer.

Gastric analysis 59 days after radiation and during the height of the patient's symptoms was not remarkable.

This case is the first in which such small radiation dosage, 2424 r at the level of the eleventh dorsal

antrum noted by x-ray study and the gastroscopic appearance of the ulcer make it likely that radiation was responsible. As pointed out elsewhere the gastric changes due to radiation have been confined to the antrum and pylorus.<sup>2</sup> In the cases studied, there was marked individual variation in sensitivity to radiation dosage. There are on record cases in which doses similar to those given in Cases 1-4 caused no gastric symptomatology. Palmer and Templeton<sup>4</sup> used radiation doses as high as 3600 r without development of ulceration, but in some cases, gastroscopically, superficial gastritis, variable in severity, was noted.

Several acidity studies were performed in Case 5, and it is noteworthy that the highest values of acidity were obtained in the second analysis at the height of the symptoms. A later gastric analysis showed marked reduction in the free acid values with concomitant symptomatic improvement. In Case 6, however, there was no such relation. At the time the first study was conducted, the patient was symptomatic, and the last two analyses were made during periods of marked improvement.

Table 3 lists 5 cases in which minimal or negative x-ray findings and symptomatic changes were present. The average radiation dose was 5000 r. The mean acidity values were, if anything, slightly higher than those in the other two groups. Again, there is no definite pattern of the acidity relative to dosage, length of time after radiation, symptoms and x-ray findings.

## DISCUSSION

Although the material used in this report is not strictly analogous to that of Palmer and Templeton,<sup>4</sup> the results are considered susceptible of comparison. With the larger dose used in our cases, the depression of acidity reported by Palmer and Templeton was not found, especially in the cases with prolonged follow-up studies. Since most of the values were obtained two months or more after com-

is regarded as having no place in the treatment of peptic ulcer. All workers in the field agree that in evaluating the results of any therapy in peptic ulcer, great caution must be exercised. The psychic effect of any kind of new therapy is well known. Thus, Sandweiss<sup>5</sup> induced remissions of symptoms in a group of patients with peptic ulcer by intravenous injection of distilled water. In the cases of Palmer and Templeton, standard Sippy neutralization was used in addition to the radiation, and the authors

TABLE 3 Data in Cases with Minimal Gastrointestinal Findings

CASE No	CLINICAL DIAGNOSIS	X-RAY DOSE	DURATION OF THERAPY days	GASTRIC ANALYSIS WITH HISTAMINE* ml	INTERVAL AFTER IRRADIATION days	REMARKS
10	Seminoma of right testis, with metastases to retroperitoneal lymph nodes	5000	86	0-95-134-156 145	533	X-ray examination disclosed minimal changes in antrum; symptoms mild.
11	Teratoma of right testicle with metastases to retroperitoneal lymph nodes	4700	79	0-5-15-95-60	107	X-ray examination negative; patient died from widespread metastases, but no involvement of stomach found at autopsy.
12	Seminoma of left testis with no metastases to retroperitoneal lymph nodes	5600	77	0-15-36 51-49	283	Symptoms mild; minimal changes noted in antrum.
13	Embryonal carcinoma of right testis with no metastases to retroperitoneal lymph nodes	5350	59	10-70-94-72 35	429	Symptoms mild; gastrointestinal x-ray examination negative.
14	Seminoma of left testis, with no metastases to retroperitoneal lymph nodes	5200	67	0-0-46-64 55	452	Symptoms mild; x-ray study not remarkable.

\*Fractional analysis with 0.5 cc of histamine; first number represents fasting specimen in units of free hydrochloric acid and other numbers specimens taken at fifteen minute intervals.

pletion of therapy, no statement regarding the immediate effect of radiation on acidity can be made. Certainly, the depression of acidity is short-lived, and the use of radiation to attain such a depression in cases of peptic ulcer, a chronic disease, therefore seems to have little place. If the effect of doses of radiation smaller than those used in this study depresses gastric acidity, it is difficult to understand why larger doses do not cause a greater depression. A possible explanation is that the radiation was directed to the antrum, whereas that in the cases of Palmer and Templeton was directed to the upper part of the stomach, the location of the major portion of the parietal cells. Palmer and Templeton also point out the extreme variability of the duration and extent of the depression of gastric secretion.

The patients in the series of Palmer and Templeton had proved peptic ulcers, whereas those in the cases discussed above were presumably free of gastrointestinal disease at the beginning of radiation therapy. Since radiation can cause definite injury to normal stomachs, it seems that an organ already the site of a disease of unknown etiology would be more susceptible to injury. No definite answer can be given to this problem, but in view of the variable effect on gastric acidity, the possibility of radiation injury to the stomach and the lack of correlation of acidity values to severity of symptoms and complications in peptic ulcer, radiation therapy

draw no conclusions concerning the efficacy of the radiation in the results obtained.

## SUMMARY

Three groups of cases with varying degrees of radiation injury to the stomach are presented. No definite pattern of effect on gastric acidity was noted in these cases.

Depression of gastric acidity two months and longer after large doses of radiation was not found.

The marked variability of response of the normal stomach to radiation, varying from perforation and hemorrhage of ulcers to no changes clinically and by x-ray examination, with similar radiation dose, was also reflected in the marked variability of free hydrochloric acid values on gastric analysis.

The use of radiation has no place in the treatment of peptic ulcer, since it has been shown that deleterious effects on the stomach can be obtained with this agent. Since the individual response is variable, the result of radiation is difficult to predict.

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## CLINICAL NOTES

PARALYSIS OF THE ABDUCENS NERVE  
FOLLOWING SPINAL ANESTHESIA\*

## REPORT OF A CASE

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THE number of cases of paralysis of the abducens nerve following spinal anesthesia reported in the literature is surprisingly small, but the condition undoubtedly occurs more frequently than is generally supposed. Although it has been reported by Dattner and Thomas<sup>1</sup> following a simple lumbar puncture, most of the cases observed followed spinal anesthesia. In 1936 Woltman<sup>2</sup> reported 2 cases following inhalation anesthesia. Hayman and Wood<sup>3</sup> presented 2 cases in 1942. Fairclough,<sup>4</sup> in a review of 2021 cases of spinal anesthesia, found that paralysis of the sixth nerve had developed in 10 cases—an incidence of approximately 0.5 per cent. This seems rather high. In the past nine months at this hospital, spinal anesthesia was performed on 379 patients with only 1 case of abducens-nerve paralysis. Many of the cases were supplemented with diluted Pentothal solution administered by the continuous drip method.

The sixth nerve is involved in about 90 per cent of all cases of paralysis of the cranial nerves. Of the many theories regarding the pathogenesis, the most plausible, which are advanced by Hayman and Wood<sup>3</sup> in their review of the etiologic factors, are mechanical, toxic and inflammatory. Adherents of the mechanical theory attach great importance to the alterations in blood and spinal-fluid pressures acting on a nerve that has a long, devious course and is in close proximity to bony structures. Fairclough,<sup>4</sup> however, states that the trochlear (fourth) is the most slender cranial nerve and has the longest intracranial course. It is difficult to see how the etiology can be laid to the toxic or inflammatory factors, since cases have been reported following a simple diagnostic lumbar tap, when no foreign agent had been instilled in the subarachnoid space,

and since the spinal-fluid findings in the majority of cases are negative.

The onset of symptoms varies from three to twenty-one days. Both eyes are equally affected. Women are more prone to develop this complication than men. The syndrome seems to follow a definite pattern and is usually preceded by headache, dizziness, stiff neck, photophobia and diplopia.

The treatment is symptomatic. An eye patch may be worn to alleviate the diplopia. Recovery takes place spontaneously within a few weeks to a few months, usually with no residual paralysis. If the paralysis persists over two years, surgical correction may be undertaken.

## CASE REPORT

A 37-year-old woman was admitted to the hospital on June 21, 1946, because of pain in the right upper abdomen of 2 years' duration. Physical examination was essentially negative. Roentgenograms showed biliary calculi, and a diagnosis of chronic cholelithiasis was made.

The patient was prepared for a cholecystectomy on July 8. Premedication consisted of 0.16 gm of morphine sulfate and 0.4 mg of atropine sulfate given subcutaneously 1 hour before operation. In the operating room the blood pressure was 130/80, and the pulse was 120. An injection of 120 mg of procaine diluted in 2 cc of spinal fluid was made between the second and third lumbar vertebrae, 20 mg of Methedrine was given intramuscularly 5 minutes before anesthesia was induced. Fifteen minutes after the spinal anesthesia the blood pressure had fallen to 90/60. The pulse was 80. An infusion of 1000 cc of 5 per cent glucose in physiologic saline solution was started. Thirty minutes after the onset of anesthesia the blood pressure was still 90/60. The patient was given 24 mg of ephedrine sulfate intravenously and 24 mg intramuscularly. Within 5 minutes the blood pressure had risen to 140/80, and the pulse to 100. The remainder of the course was not remarkable, and the patient was returned to bed in good condition.

Three days after operation the patient complained of severe headaches that lasted for 2 days. On the 6th postoperative day the patient still had slight headaches but also complained of double vision. At that time a convergent strabismus of the right eye was noted. The pupils were equal and slightly dilated, but reacted normally. Eye consultation confirmed the finding of paralysis of the right sixth cranial nerve. No treatment was advised.

The patient left the hospital on the 21st day after operation, when function of the right external rectus muscle was almost normal.

## SUMMARY

A case of unilateral paralysis of the abducens nerve following spinal anesthesia is reported. Recovery was practically complete at the end of three weeks.

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# A COMPARISON OF THE VALUE OF THE RECTAL SWAB AND THE FECAL SPECIMEN IN CULTURING STOOLS\*

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THE widespread use by the armed forces in recent years of the rectal-swab technic for obtaining material for stool culture, described by Hardy, Watt and DeCapito,<sup>1</sup> has emphasized the value of this method in the study of large numbers of cases in epidemics of diarrheal disease and in the survey of food handlers. This technic is simple, easy to perform and readily adaptable for use in the home, office and hospital. Individual swabs in sterile test tubes assure immediate collection of material, aid in its prompt arrival at the laboratory and eliminate many of the cumbersome and unpleasant phases of the collection of the conventional fecal specimen. Whether or not the results of this method are comparable to those of an older, established procedure is important for complete evaluation of its efficiency. This study compares the results of stool cultures taken by the rectal swab and the conventional fecal specimen methods.

Rectal swab and fecal specimens taken on the same day were examined in 31 student nurses. Within two hours after collection the material obtained by these methods was inoculated onto eosin-methylene-blue agar and on *Salmonella-Shigella* agar (Difco). Two plates of each medium were used in all cases. After incubation at 37°C for twelve to twenty-four hours, the growth of coliform and colorless colonies was noted. The latter were inoculated into dif-

ferential mediums. Identification of the organisms was based on biochemical characteristics and, whenever possible, on serologic reactions.

Coliform colony growth resulted from inoculation by both methods in 29 of the 31 cases. There were no colonies on the plates from the swab in 1 case in which there was fair coliform growth from the fecal specimen. In another case no growth on any plates followed inoculation by both methods. In general coliform colonies were more abundant on the plates from the fecal specimen. No constant relation between the amount of material on the swab and the resulting colony growth was noted.

Nonlactose-fermenting organisms were isolated from the colorless colonies present in 6 of the 31 cases. In 2 of these cases the swab and the specimen showed almost identical results. *Proteus mirabilis* and a paracolon intermediate<sup>2</sup> were recovered by both methods in 1 case. In the other, *Pr. mirabilis* and *Pseudomonas aeruginosa* were present, *Pr. mirabilis* being isolated, in addition, from the fecal specimen. There were 3 cases in which colorless colonies appeared only on the plates inoculated with the rectal swabs. A paracolon intermediate was identified in two of these and a paracolon *Aerobacter*, a variant of Type 37711,<sup>3</sup> was found in the other. The remaining case showed the presence of a paracolon *Aerobacter*, Type 32011,<sup>3</sup> in the fecal specimen.

\* \* \*

Under the conditions of this study, the rectal-swab method and the conventional fecal-specimen method appear to be of comparable value in culturing stools.

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## MEDICAL PROGRESS

### GYNECOLOGY: THE VAGINAL SMEAR

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THE mammalian female genital tract is lined throughout with epithelium that grows and recedes in response to alterations in the concentration of ovarian hormone<sup>1</sup> In the vagina, cyclic changes are described that include variations in the activity of the basal layer, in the thickness of the epithelium and in the maturity (cornification) of the squamous cells at the surface<sup>2,3</sup> Like epithelium elsewhere, the vagina undergoes continuous desquamation A random sample of the fluid present at a given time contains cells recently shed from various parts of the genital canal, together with leukocytes, erythrocytes, bacteria and mucus

Stockard and Papanicolaou<sup>4</sup> made a careful study of the vaginal cytology in the guinea pig and correlated it with anatomic and histologic findings in the uterus and ovaries They concluded that four stages of the sexual cycle and the time of ovulation could be detected with accuracy through the medium of the vaginal smear Identical observations have been made in rats and mice

Although similar changes were observed in monkeys,<sup>1</sup> there was less marked cyclic variation than in rodents The vaginal smear could not be used as a dependable index of the date of ovulation, or even to tell whether ovulation had taken place<sup>5</sup> This difference between rodents and higher forms is apparently closely related to the disappearance in the latter of a specific short period of estrus with the extreme degree of vaginal cornification seen, for example, in the rat

#### TECHNIC

Material for examination may be obtained directly from the vagina or from the blade of a bivalve speculum if no lubricant has been used The secretion is transferred to a glass slide by means of a cotton swab, wire loop or pipette Many use the simple method described by Papanicolaou<sup>2</sup> of direct vaginal aspiration with a rubber suction bulb attached to a length of dry glass tubing Effective suction can be exerted if the tip of the pipette has been flamed down to a lumen of capillary size. Material is expelled on a glass slide, spread thin with the tip of the pipette, and placed at once in a fixative solution of equal parts of 95 per cent ethyl alcohol and ether Various stains have been devised A trichrome stain<sup>6</sup> has been most effective

in bringing out nuclear detail Details of preparation and staining are completely described in several publications<sup>2, 6, 7</sup>

#### INTERPRETATION BASED ON VARIATIONS IN THE RELATIVE NUMBER OF NORMAL CONSTITUENTS

Papanicolaou<sup>2</sup> reported the first careful studies on the vaginal smear in human beings He described definite cyclic variation in both epithelial and blood constituents and traced analogies with the cycle in rodents After menstruation he observed a steady increase of cornified epithelial cells with a decrease in leukocytes and a "clean" appearance to the smear With ovulation there is a tendency for the epithelial cells to curl and clump and for leukocytes to reappear in large numbers A few erythrocytes are often noted at this time Between ovulation and menstruation, changes in the vaginal cytology are less constant With menstruation, of course, the outstanding finding is the presence of erythrocytes in great numbers Definite alterations in pregnancy are also described — chiefly, an increase in the size of the cells and the appearance of large flat cells Some correlation with ovarian histology was possible in 17 patients who came to operation during the course of the investigation

Heller and his co-workers<sup>8</sup> were able to examine the uterus and ovaries in 28 women who had been studied by means of vaginal smears before and after operation They found the smear an unreliable index of the state of the ovaries A critical review of various reports<sup>2, 5, 8, 9</sup> justifies the conclusions of Neustaedter and Mackenzie<sup>10</sup> that for practical purposes the vaginal smear usually yields correct information only regarding estrogen elaboration during the proliferative phase of the cycle The smear is difficult to evaluate during the progestational phase and gives no definite indication of corpus luteum action and therefore no clue concerning whether or not ovulation has taken place Rakoff<sup>11</sup> is substantially in agreement, although he says that "the experienced observer often can note changes in the day-to-day smears suggestive of corpus luteum function as well"

Reports on the use of the vaginal smear in abnormal menstrual states are rare Shorr and Papanicolaou<sup>12</sup> suggest a reclassification of the amenorrheas into three groups one showing repeatedly the atrophic smears of ovarian inactivity, another demonstrating continuous low-grade estrin effect

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and still another exhibiting cyclic variations without overt menstruation. They cite a case treated with gonadotropic hormone with conversion of the smear to the follicular type and menstruation. There was nothing to suggest that ovulation had occurred, however. Using women with well established menopause, both clinically and by smear, Shorr<sup>12, 14</sup> studied the effect of androgen and progesterone on the vaginal cytology. The male sex hormone failed to alter an atrophic smear, although it reduced the urinary prolan excretion to normal levels. Moreover, it caused reversion of the estrogen-induced proliferative smear to the atrophic type, even with continuation of estrogen therapy. Progesterone given with estrogen produced changes in the smear comparable to the postovulatory phase of the menstrual cycle. Most workers, however, have found it impossible to evaluate or control progesterone therapy by means of smears, and Mack<sup>7</sup> in a comprehensive review concludes that only degrees of estrogen effect can readily be distinguished by the smear technic.

It is obvious that the menopausal state is the one most easily detected in the vaginal smear. Characteristically, there is almost complete disappearance of superficial cornified cells.<sup>15</sup> Cells from deeper and basal layers are much in evidence, together with many leukocytes. The administration of estrogenic drugs in the majority of patients converts an atrophic smear into one showing full cornification. Unfortunately, some degree of estrogenic effect is apparent in the smears of many patients with well established clinical menopause. No consistent correlation between the appearance of the smear and the urinary excretion of gonadotropic hormone is manifest<sup>3</sup> or with symptoms either before or after therapy.<sup>1, 16</sup> Although the smear cannot be used as a delicate control for estrogen therapy, it will reveal whether, in a patient with symptoms suggestive of the climacteric, there is concomitant vaginal atrophy and whether, after treatment of a patient with estrogen fails to obtain relief of symptoms, a physiologic effect has been produced — that is, whether medication has been taken as directed and is being utilized (metabolized) in a normal fashion.

The response of the atrophic vaginal mucosa to estrogen readily suggests itself as a simple method of hormone assay in every way comparable to that used in animals.<sup>7</sup> Both the study of cytologic detail and the less painstaking glycogen index have been applied in this connection. The method is reliable in determining comparable potencies of various estrogens by successive trial in the same woman, but the amount of any one estrogen needed to produce the same vaginal changes in other castrate women shows marked variation.<sup>18</sup> Similar results are reported in experiments on the antiestrogenic effect of androgens.<sup>13</sup>

#### INTERPRETATION BASED ON THE PRESENCE OF ABNORMAL CONSTITUENTS

While observing and classifying the cell types found in human vaginal smears, Papanicolaou<sup>17</sup> occasionally noted conspicuous cells that failed to conform to any previous characterization. These were in patients with cancer of the genital tract. After the accumulation of a large body of evidence, a solid foundation was laid for the cytologic method of cancer diagnosis.<sup>18</sup> Facility in the detection of abnormal cells depends, of course, on complete familiarity with normal cytology.

Criteria of abnormality are a variation in nuclear size and staining properties and an increase in nucleus relative to the cytoplasm.<sup>18, 19</sup> The cells tend to occur in clumps, and individual outlines are often indistinguishable. Leukocytes are abundant. Malignant giant cells are described, and must be distinguished from benign multinucleated cells. In the more differentiated lesions unusual forms, such as "tadpole" and "fiber" cells, may be encountered. Comparison between the vaginal smear, a smear taken directly from the tumor and the pathological section of the tumor<sup>19</sup> shows a morphologic resemblance between the cells that is strong presumptive evidence of a common origin.

Errors associated with the method are of two types: cancer in the presence of a negative smear and cases in which the smear is positive but no cancer can be found. The first error is inherent in the method, since no tumor cells can be seen if none are present on the slide. Papanicolaou and Marchetti<sup>20</sup> suggest taking smears directly from the cervical canal and endometrium to reduce the likelihood of this mistake. Final judgment regarding errors of the second type must await a series studied by serial section of all available operative and post-mortem material. Biopsy, curettage and even routine pathological examination, as Mallory<sup>21</sup> points out, may miss small lesions. A review of reported series reveals that about 6 per cent of patients with cancer of the cervix have negative smears, whereas cancer of the endometrium is missed in about 15 per cent of cases.<sup>18, 22-24</sup> Of patients in whom cancer cannot be found, between 1 and 2 per cent have what are reported to be positive smears.

Increasing interest in the technic has been stimulated by two facts. In the first place the universal applicability and the ease and rapidity with which the smear can be taken make it ideal for screening large groups of persons. Secondly, every published report includes protocols of patients in whom positive smears called attention to cancer before it had given the slightest hint of its existence. Even carcinoma *in situ* has been detected in this fashion.<sup>22, 23, 24</sup> It should be noted that the method is finding ready application in the diagnosis of cancer of the bronchus, stomach and urinary tract.<sup>18</sup>



Graham<sup>27</sup> recently described and discussed the significance of changes observed in the vaginal cytology of women receiving radiation therapy for carcinoma of the cervix. Characteristic increase in cell size, vacuolization and abnormal nuclear growth and degeneration were seen in the normal as well as the malignant constituents. In a group of patients showing good radiation response by Graham's criteria, the short-term results of therapy were strikingly better than those in a similar group that had shown a poor response to radiation. This observation offers promise of a new and exceedingly valuable application of the vaginal smear. A variety of radiologic attacks on the disease can be assessed without the need of three-year or five-year clinical results. Moreover, heroic surgery may eradicate occasional moderately advanced cervical cancers, if a method of selecting cases with a poor prognosis under radiation treatment is devised.

A final use for the smear should be mentioned. In the cancer follow-up clinic it affords a simple check on the clinical impression regarding local recurrence of disease. This is particularly important in cases in which extensive adhesions and atresia make adequate examination impossible. Approximately 13 per cent of a series reported by Meigs et al.<sup>22</sup> fall into this category, and among their cases is one of a patient in whom, after radiation for cancer of the cervix, positive smears were found consistently for seven months before biopsy confirmation could be obtained.

### CONCLUSIONS

The vaginal smear is a simple, painless and universally applicable method of observing and recording certain changes in the status of the female internal genitalia.

Degrees of estrogenic effect can be distinguished in the vaginal smear.

By means of day-to-day smears, an experienced observer can also occasionally draw conclusions regarding corpus-luteum function.

In cancer of the genital tract, the smear is of help not only in diagnosis but also in prognosis and in the detection of persistent or recurrent disease.

264 Beacon Street

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CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*BENJAMIN CASTLEMAN, M.D., *Associate Editor*EDITH E. PARRIS, *Assistant Editor*

## CASE 33281

## PRESENTATION OF CASE

A twenty-six-year-old draftsman was admitted to the hospital complaining of recurrent attacks of painful swelling of the joints.

At the age of fourteen attacks of swelling and pain in the joints developed. They first involved one ankle and subsided spontaneously after a few weeks, without residua. Later during the same year, however, the knees became swollen and stiff. The patient was thought to have rheumatic fever and was put to bed for nine months. During that time he had several recurrences but was finally allowed to return to school after a short period of freedom from symptoms. Thereafter, he was never free from attacks for long. The swelling and pain later involved the knees, ankles, hips, wrists, elbows, shoulders and fingers. There was never any known precipitating cause. The joints became swollen, painful and stiff, improving symptomatically with aspirin therapy. In the early stages of the illness no permanent changes of the joints were noted. The patient was able to complete high school but absence from classes necessitated by the illness forced him to leave college. Six years before admission he was studied in New York City for three months and given a course of each of the new sulfonamides without effect. The knee was tapped at that time, and a pleomorphic streptobacillus was isolated. From this organism a vaccine was made and injected, also without effect. Many attacks continued each year, with minimal aches and pains between major flare-ups. Four years before admission the patient noticed stiffness and limitation of motion of the right hip that did not subside after an attack. He moved to the Southwest for a change in climate, but the course continued unchanged, with periodic attacks. He returned to New York City, where several acute episodes were treated with courses of gold and Ertron without noticeable benefit or toxic effect. During the year before entry he felt well, having about ten months with no symptoms other than the stiffness of the right hip. About four months before admission a recurrence worse

than any previous attacks occurred, with marked swelling of the right knee and less severe involvement of all the other joints. Six weeks later he was seen for the first time in the Out Patient Department, where he showed some residual involvement of both knees and the left temporomandibular joints, as well as a 15° permanent flexion of the right knee with marked limitation of motion. Three weeks later the right knee was tapped, and 50 cc. of cloudy yellow fluid was withdrawn, analysis of which showed 5750 white cells per cubic millimeter with 66 per cent neutrophils, 18 per cent lymphocytes and 16 per cent monocytes, the sugar level was 132 mg per 100 cc (serum, 125 mg per 100 cc), cultures, including one for pleuropneumonia-like organisms, were negative. Examination of the urine showed a +++ test for albumin. No enlargement of the thyroid gland was noted at that time. The knee swelling gradually subsided while the patient remained at home in bed. Three weeks before admission he had an attack of "grippe" with fever, the temperature ranging up to 104°F, and with cough and malaise. There was no chill or sore throat. He was seen by a physician, who noted that the thyroid gland was five times its normal size. The patient had not noticed this obvious swelling of the neck, since it had caused no pain and he had worn no collar while bedridden for the previous ten weeks. His fiancée believed that it had been present before the onset of the febrile illness. There was no tenderness over the thyroid gland and no symptoms of pressure or constriction. The temperature gradually came down with treatment by oral penicillin. There was a loss of appetite and perhaps some weight loss, but the amount was not known. The patient had been under emotional tension owing to the flare-up of the disease, loss of his job and so forth, but he had had no excess of sweating, tremor, diarrhea, intolerance to heat or increase in the prominence of the eyes. No history suggestive of an intake of goitrogenic substance could be elicited. At the time of admission the patient considered the thyroid gland to be somewhat smaller than it had been when the enlargement was first noted.

There was no family history of arthritis or thyroid disease.

Physical examination revealed a well developed man in no distress. The skin was somewhat pale but not excessively moist. No superficial lymph nodes were palpable. The eyes were prominent, with no lid or globe lag. The thyroid gland was diffusely enlarged six to eight times the normal size, the right lobe being larger than the left. Several examiners were able to feel the pyramidal lobe. The gland was firm but not hard and slightly irregular in outline without fixation, tenderness or bruit. The musculature of the arms and legs showed considerable atrophy. No swelling, tenderness or limita-

tion of motion of any joints other than that of the right hip was noted. The fingers showed a spindle deformity. Examination of the heart, lungs and abdomen was negative.

The temperature was 97.2°F, the pulse 85, and the respirations 17.

Examination of the blood disclosed a red-cell count of 5,100,000 and a white-cell count of 14,000, with 71 per cent neutrophils, 23 per cent lymphocytes, 4 per cent monocytes and 1 per cent eosinophils and basophils. The hematocrit was 38 per cent, and the sedimentation rate 1.22 mm per minute. On several analyses the urine gave ++ and +++ tests for albumin, with specific gravities from 1.008 to 1.020 and no sugar, and the sediment contained occasional hyaline and granular casts, 3 to 6 red cells and 5 to 10 white cells per high-power field. The nonprotein nitrogen was 16 mg, the cholesterol 263 mg, and the total protein 6.3 gm per 100 cc, the protein-bound iodine being 5.0 microgm per 100 cc. A Congo-red test showed 51 per cent retention. The basal metabolic rates were -9 and -10 per cent. A radioactive-iodine-excretion test was normal, with 69 per cent excretion within forty-eight hours.

X-ray examination of the chest was negative, and intravenous pyelograms were normal.

In the hospital the patient's condition remained unchanged. A biopsy of the thyroid gland was taken on the twenty-first hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES: The last statement indicates that the diagnosis was probably made from the biopsy of the thyroid gland, although we have no assurance that that was so. Possibly, something was found that led to subsequent treatment or operation about which we are not told. But since this patient was in fairly good condition on admission, I suppose that he survived the biopsy and therefore assume that the diagnosis is to be narrowed down essentially to the lesion of the thyroid gland.

May we see the x-ray films? Although examination is reported to have been negative, there are one or two things that I think should be brought out. I am particularly interested in knowing whether any enlarged mediastinal lymph nodes were demonstrated—I am keeping in mind the possibility of thyroid lymphoma.

DR STANLEY M. WYMAN: The films of the chest show the lung fields to be clear. The heart shadow is not remarkable. There are no visibly enlarged mediastinal or hilar nodes. The plain film of the abdomen shows the liver edge to be within normal limits. The spleen may be wider than usual.

DR KRANES: Do you think that the spleen is enlarged?

DR WYMAN: Possibly so, but there is no good x-ray evidence. It is wider than usual, but not definitely enlarged.

There is scoliosis of the lumbar spine to the right. The kidneys are not remarkable. There are definite arthritic changes about both hip joints, with narrowing of the joint spaces. There is some pseudocyst formation. The sacroiliac joints are also somewhat cloudy. The renal function is good, with satisfactory excretion of the dye. The calyces, pelvis and ureters are not remarkable. The bladder shadow is not visualized.

DR KRANES: I was interested in two things: whether there was any enlargement of the mediastinal lymph nodes and, in view of the albuminuria and hematuria, how well the intravenous dye was excreted.

I cannot explain why the thyroid gland increased so rapidly in size. Possibly, it did not grow so fast as the record indicated. Perhaps the failure to note it at the time of the examination in the Out Patient Department was due to the facts that at that time more interest was concentrated on the joints and that the thyroid gland was not carefully examined. A thyroid gland five or six times the normal size, however, should be reasonably apparent. Nonetheless, it is slightly difficult for me to believe that the gland increased so rapidly—actually within two months. It would be of some interest to know whether the physician who noticed the original enlargement was the one who had seen the patient right along. If so, this observation would carry more weight. It is interesting that the patient himself was not aware of the considerable enlargement of the thyroid gland—a phenomenon that we often run into.

What diseases of the thyroid gland will lead to rapid enlargement? The most frequent, of course, is Graves's disease, in which the goiter may appear quite rapidly, although it usually does not. Certainly, this history does not suggest Graves's disease. All the evidence we have indicates that the goiter was nontoxic. The physical examination and the laboratory evidence are against Graves's disease, which must therefore be excluded.

Another cause of rapid enlargement of the thyroid gland is acute inflammation. I wondered whether the acute febrile episode during which the gland was first noted was due to acute thyroiditis. If it was, I do not see how it is possible to make such a diagnosis in the absence of all the signs that usually accompany that condition—pain, tenderness and heat. There was swelling, to be sure, but none of the other evidences of inflammation, and without them I cannot seriously entertain the diagnosis of acute thyroiditis, although that would explain the rapid enlargement of the gland.

Another possibility to be considered is malignant tumor, although the description of the gland certainly does not suggest it. Carcinoma, I think, is extremely unlikely because of the patient's age and the fact that the thyroid gland was diffusely enlarged. I should think that a malignant thyroid

gland of this size would have been more adherent to surrounding structures, as well as irregular and nodular. The same objections, however, do not hold for lymphoma. I do not see how one can exclude lymphoma of the thyroid gland except that there is no evidence of it anywhere else in the body. And to make that diagnosis without any confirmatory evidence is rather hazardous.

The most frequent cause of gradual enlargement is the ordinary colloid goiter. But there are a number of objections to that. If this had been colloid goiter one would expect the enlargement to have been present for many years. More important than anything else, I find it hard to believe that I should have been asked to discuss a colloid goiter at a clinicopathological conference. It is such an extremely commonplace condition with so little clinical or pathological interest that I exclude it for that reason more than for any other.

Against chronic thyroiditis is the description of the gland, which does not fit with either the Riedel or the Hashimoto type of chronic thyroiditis. Such glands are usually extremely hard, often described as ligneous, and usually adherent to surrounding and underlying tissue, frequently causing pressure symptoms. The Hashimoto type is extremely rare and is practically excluded in this case, because of the sex, being almost exclusively confined to women. Since the gland in the case under discussion was firm but not really hard and not adherent to the other structures the diagnosis of chronic thyroiditis is quite unlikely.

Let us for a moment pass on to a discussion of the arthritis to see if we can obtain a clue there. I assume that it was rheumatoid arthritis. Certainly, the therapy prescribed over many years leads one to that belief. It is unusual, however, to see so little joint involvement in a patient who has had severe rheumatoid arthritis for twelve years. — I should have expected a great deal more. Ordinarily, one does not think of rheumatoid arthritis as being a cause of enlargement of the thyroid gland, but we might search around for certain complications of rheumatoid arthritis, the most frequent of which is amyloid disease. I am rather inclined to believe that the patient did have amyloid disease, chiefly because of the presence of albuminuria and of slight hypercholesterolemia and probably also because of the Congo-red test. — I might say that the Congo-red test described in this case is certainly not diagnostic. I imagine that Dr. Ropes will disagree with me on that, but I believe that a not inconsiderable number of normal people have 50, 60 or even 70 per cent disappearance of the dye from their blood within an hour. An interesting discussion of this problem has recently been published.<sup>1</sup> I should also add that in patients with albuminuria the results must be interpreted with caution, since some of the dye is excreted in the urine. Unless one collects the urine during that

hour, one may get a false-positive test. Nevertheless, because of the fact that this patient had rheumatoid arthritis over a twelve-year period, as well as a persistent albuminuria, a hypercholesterolemia and a suggestive Congo-red test, I assume that he had renal amyloidosis. The usual sites of amyloid deposit are the kidneys, the liver, the spleen, and the adrenal glands, although it may appear in any other part of the body.

The thought occurred to me that if this patient had amyloidosis, he might also have had amyloid deposits in the thyroid gland. I had never heard of such a condition but I decided to look it up. I found an interesting article by Walker,<sup>2</sup> of Kansas City, in which he reviewed the literature describing 58 cases of what he called "amyloid goiter." In these 58 cases, only 35 patients presented true goiters. Two of these were operated on because of thyroid enlargement. I should like to suggest that as a possibility in the case under discussion. I realize that it is rather foolish to suggest a diagnosis of which one has never heard, but perhaps it is not always wise to be logical. Probably the main reason I came to that conclusion was that the presentation of thyroid problems was so unusual that the case had some sort of special interest.

DR. TRACY B. MALLORY: Will you tell us how the opinion ran on the wards?

DR. LEWIS K. DAHL: I must say that no one made the astute diagnosis that Dr. Kranes has just given. I do not believe it would add much to go into detail as to what we thought because it was so varied. No one really made the diagnosis.

DR. BERNARD JACOBSON: I do not believe the patient was too young to have a completely asymptomatic thyroid carcinoma. I also do not believe that albumin per se was the cause of excretion of Congo red in the urine. I think that albumin is present only when there is a nephrotic element. I am interested to know what the excretion in the urine was during the Congo-red test, if it was done. Do you know what the albumin-globulin ratio was in this last serum protein determination?

DR. MALLORY: The ratio was 1:28.

DR. RULON W. RAWSON: In the Thyroid Clinic there were two schools of thought. One was that this man had Hashimoto's struma, and the other that it was something that we had never seen before.

DR. KRANES: Despite the sex?

DR. RAWSON: We have seen Hashimoto struma in men.

DR. KRANES: How often?

DR. RAWSON: I cannot give the figures, but we have seen it.

DR. MALLORY: The ratio of women to men is about 4:1 in the cases that we have seen.

DR. RAWSON: The diagnosis of lymphoma was entertained, in spite of the fact that it was not written down, but we found nothing else to support it. I was among the group that did not know what

it was I should like to comment on the statement that cancer is rare at this age. We see more cancers of the thyroid gland in the younger age groups than in the older, but the tumor is usually a discrete nodule rather than a diffuse goiter. A true cancer of the thyroid gland in a large goiter such as this patient had is unusual in the young age group. On the basis of the clinical picture I believe that the diagnosis of cancer can be discarded.

Dr Robertson, will you tell us your findings at operation?

DR CHARLES ROBERTSON At operation we exposed the isthmus of the thyroid gland and were at once impressed by the unusual color of the glandular tissue, which was pale, pinkish and quite vascular but did not seem to be the site of an inflammatory process because the tissues overlying it were freely movable, with no adherence to the surrounding fascial planes The right lobe, as described in the physical examination, was somewhat larger than the left The whole thyroid gland, however, seemed to be involved in this diffuse process, whatever it happened to be We satisfied ourselves that the appearance in the isthmus was typical of the whole gland and removed the isthmus for biopsy On section the gross appearance was more like that of the parotid gland or a soft specimen of the pancreas

## CLINICAL DIAGNOSIS

### Subsiding acute thyroiditis

### DR KRANES'S DIAGNOSIS

### Amyloid goiter

## ANATOMICAL DIAGNOSIS

### Amyloid goiter

## PATHOLOGICAL DISCUSSION

DR MALLORY The biopsy specimen that we received was divided into two portions, of which one came to our laboratory and the other was sent to the Thyroid Laboratory for special study. Examination of the specimen that we received disclosed few acini of thyroid tissue and a large amount of ordinary adipose tissue, with mature fat cells and a small amount of fibrous tissue between the fat cells. When the second portion was examined histologically, it was evident that the fibrous tissue between the fat cells was hyaline and homogeneous in character, and when that was stained with methyl violet it was found to be full of amyloid. This called our attention to something that none of us was familiar with. In cases of amyloidosis of the thyroid gland it is not unusual to find large amounts of adipose tissue constituting part of the goiter. This was well described by Wegelin<sup>3</sup> in his monograph on thyroid disease.

There is nothing in the presence of amyloid disease to rule out

course, but we can assume that the biopsy was representative. A major part of the enlargement of the gland was due to adipose tissue and not directly to amyloid deposit, but the combination of massive development of adipose tissue in the gland along with amyloid infiltration occurs too frequently for coincidence. We do not know what the relation is, but there is evidently one.

DR KRANES In the cases reported by Walker, that is also mentioned

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## CASE 33282

## PRESENTATION OF CASE

A fifty-six-year-old machinist entered the hospital because of jaundice

Two years before admission severe pain in the right upper quadrant and jaundice developed, and a cholecystectomy was performed at another hospital, where a gall bladder containing many stones was removed. After the procedure the patient was told that the liver was enlarged. The jaundice cleared slowly over a period of two or three months, but he continued to have intermittent bouts of right upper quadrant pain and jaundice, with light stools and dark urine for six months. Then he was able to go back to work, and was able to have an occasional bout of pain during the following year and a half. On his next admission the patient suffered severe pain in the

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negative except for the presence of clay-colored stools

The temperature was 100.5°F, the pulse 120, and the respirations 25. The blood pressure was 120 systolic, 70 diastolic.

Examination of the blood disclosed a red-cell count of 4,200,000, with a hemoglobin of 12.2 gm., and a white-cell count of 30,100, with 85 per cent neutrophils, 6 per cent lymphocytes and 9 per cent monocytes. The urine gave a ++ test for albumin and a +++ test for bile, and the sediment contained numerous coarsely granular casts, rare red cells and 8 white cells per high-power field. The stools were gunmetal color and slightly positive for bile and gave 0 to + guaiac responses. The serum bilirubin was 12.6 mg per 100 cc direct and 16 mg indirect, and the nonprotein nitrogen was 19 mg per 100 cc. The protein level was 6 gm per 100 cc, and the chloride 80 milliequiv per liter. The prothrombin time was 20 seconds (normal, 15 seconds). The amylase was 29 units per 100 cc.

Seven hours later the abdomen was markedly distended and tympanic but still not tender. Peristalsis was active.

A plain film of the abdomen demonstrated dilatation of the large bowel, which contained several scybala. Gas appeared to stop abruptly at the distal descending colon; none was seen in the sigmoid or rectum. There were several gas-filled loops of small bowel. The pelvis showed homogeneous soft-tissue density, which was thought to be compatible with a filled bladder. In the chest film the right lower lobe appeared atelectatic and diminished in size.

On the day following admission the patient's condition was considerably worse. The jaundice was deeper, and cyanosis developed. The coarse rhonchi had increased, and on the right wet bubbling rales were also heard. He was receiving penicillin and digitalis. He began to complain of pain and tenderness to the left of the umbilicus. The pain was intermittent and crampy. No spasm was associated with this tenderness, which extended over most of the left side of the abdomen and was more marked above than below. Distention increased despite a Miller-Abbott tube, the patient had passed no gas and only moderate amounts of feces by rectum. Peristalsis could not be heard. Later during the same day the blood pressure was 74 systolic, 35 diastolic.

In an oxygen tent the cyanosis was considerably relieved. By the third day the distention and tenderness were much improved, and the temperature, pulse and respirations were down to normal. The phosphatase level at that time was 12.3 units per 100 cc.

Another film of the abdomen revealed a generalized homogeneous area of increased density.

The urinary output had been steadily declining from 1200 to 500 cc, although the intake of fluid remained at 3000 cc daily.

On the fourth day all the improvement was lost, and the patient became sicker than ever. The temperature spiked to 102°F. The nonprotein nitrogen reached 98 mg per 100 cc. He was dyspneic and disoriented and pulled out the Miller-Abbott tube. The abdomen, however, remained soft and non-distended, and peristalsis was again audible. The liver had increased in size, occupying the whole upper abdomen.

The patient became comatose, with labored respirations, and died on the fifth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR J SYDNEY STILLMAN: May we see the x-ray films? I am particularly interested in finding out if "scybala" is Latin for "red herring."

DR TOUFIC KALIL: These films were taken after the Miller-Abbott tube had been inserted.

DR STILLMAN: This shadow, I assume, represents one of the scybala.

DR KALIL: There is one in the splenic flexure and one in the descending colon.

DR STILLMAN: Where is the atelectasis?

DR KALIL: The atelectasis surrounds one of the bronchi to one of the divisions of the lower lobe. The open bronchus is within the atelectatic area.

DR STILLMAN: We must first determine the nature of the liver disease from which this man suffered for two years before death, and then we must explain the cause for his rapid decline in the last of many attacks of right-upper-quadrant pain and jaundice.

We are told that two years before admission a gall bladder containing many stones was removed at another hospital and that at operation the liver was found to be enlarged. We do not know how long he was jaundiced prior to that operation, whether the common duct was explored at the time of operation or whether the spleen was found to be enlarged.

The jaundice cleared extremely slowly, indicating that the operation had failed to relieve the obstruction or the hepatic disease causing the jaundice. For the reasons that I shall present, I favor obstruction of the bile ducts by a stone or stones as the initial cause of the chain of events that led to this patient's death.

In the initial attack of jaundice, severe pain in the right upper quadrant was prominent. Many stones were found in the gall bladder, so that there was at least one chance in four that there were stones in the bile ducts also. There is no evidence that the duct was explored. Even if it had been explored we are familiar with the fact that stones are left behind in the exploration of the common duct even by the best of surgeons—the figure varies from 16 to 33 per cent of patients explored.

The subsequent course was compatible with intermittent obstruction due to stone. The man, a machinist, returned to work and presumably stayed at it. He maintained his usual weight. Occasionally,

however, he had attacks of pain in the right upper quadrant and jaundice, which apparently were not long lasting. Absence of chills and fever in the triad of Charcot is not unusual, since they are not present in two thirds of these bouts. Although itching is usually associated with obstructive jaundice, it is present in only 50 per cent of cases and in slightly less than that in parenchymatous disease of the liver. Pruritus is therefore not a real diagnostic point.

In the final attack of jaundice the first symptom was colicky pain in the right upper quadrant. The jaundice became intense, and in five days the patient became seriously ill. He was dehydrated and feverish. The liver was enlarged. There was evidence of intestinal obstruction, which I shall pass over for the present. There was a high white-cell count, as well as albumin and formed elements in the urine. The serum bilirubin was higher than one would expect in straightforward obstructive jaundice, particularly of this duration. The alkaline phosphatase was markedly elevated, which is consistent with obstructive jaundice. The prothrombin time was increased.

Because of the rapidly fatal course during this attack of jaundice it is necessary for me to consider that some additional factor adversely affected the liver. Many previous attacks, some long lasting, had occurred without causing liver failure. It seems logical to me to assume that this additional factor was an infection of the obstructed bile ducts, leading to added diffuse damage to the liver parenchyma. This complication of intermittent obstruction of the bile duct is not infrequently seen and could well explain the fever, the high white-cell count and the rapid development of the hepatorenal syndrome, which caused the patient's death. The temporary improvement might be attributed to the effect of penicillin on an undrained infection in the liver and also to a pneumonic infection. In addition, he had symptomatic relief of the intestinal obstruction, which I believe was precipitated by the scybala. The patient had been eating little as a result of the nausea accompanying this attack of pain and jaundice. He had been receiving morphine. He had not passed any fecal material. As a result of the impaction and the shock-like state, I think that he then developed intestinal obstruction, which, at least symptomatically, was relieved by the Miller-Abbott tube. Eventually, however, the liver failed as a result of the damage over a two-year period of biliary cirrhosis, the acute damage from the fresh attack of stoppage of the flow of bile and the final insult of infection. Ascites probably developed because the damaged liver was unable to inactivate the anti-diuretic hormone. Owing to the combined kidney and liver damage, the poorly understood chemical changes of the hepatorenal syndrome developed, causing death in liver disease.

I discarded the possibility that the initial attack of jaundice was due to portal cirrhosis, infectious hepatitis or some other form of liver disease because of the lack of supporting evidence in the history, physical examination and subsequent course and also because of the necessity of considering the gallstones as a purely incidental finding. I wondered whether the surgeon who operated on this man believed that the enlarged liver was really the cause of the jaundice and therefore did not search further for a possible obstruction in the common duct, either at the time of operation or later. Because a satisfactory explanation for the obstruction was at hand and because of the lack of positive supporting evidence, I did not seriously consider other causes of obstruction, such as parasites and neoplasm, primary or secondary. My diagnoses are therefore obstructive jaundice due to choledocholithiasis, biliary cirrhosis, suppurative cholangitis, biliary nephrosis, atelectasis of the right lower lobe and probably a terminal pneumonia.

DR WALTER BAUER. I agree with all the diagnoses that Dr Stillman has made, but wonder if we should entertain the possibility that a common-duct stone had eroded and that this man had a bile peritonitis, slight to begin with, but becoming severer — another explanation for the phenomena, including the dilated bowel, that were observed.

DR STILLMAN. I considered bile peritonitis but thought that there would have been other signs of peritoneal irritation, which were not reported. There were localized areas of tenderness, but shortly after the obstruction had been symptomatically relieved the abdomen became soft to palpation, which would be unlikely if perforation with subsequent bile peritonitis had taken place.

DR BAUER. One thing to remember is that the Miller-Abbott tube sometimes changes the clinical picture.

DR ROBERT R. LINTON. I think that it does in true mechanical obstruction but not in peritonitis.

DR TRACY B. MALLORY. It takes a rather large gallstone to produce gallstone ileus.

DR BAUER. I was not thinking of gallstone ileus — rather of a gallstone eroding through the common duct into the peritoneal cavity, with consequent bile peritonitis.

DR LINTON. That is usually such a slow process that the structure around the point of perforation seals itself off, so that peritonitis rarely occurs. We do not see many cases of fatal peritonitis due to this cause.

I was surprised that this man died as rapidly as he did. It is also interesting that the liver was so large, and I wonder if he had a hepatic-vein thrombosis. I do not know how one could prove it, but it is a possibility that I thought of, having seen such a case recently.

## CLINICAL DIAGNOSES

Bile-duct obstruction  
Biliary cirrhosis  
Uremia  
Bronchopneumonia

## DR. STILLMAN'S DIAGNOSES

Obstructive jaundice, due to choledocholithiasis  
Biliary cirrhosis  
Suppurative cholangitis  
Biliary nephrosis  
Atelectasis right lower lobe  
Terminal pneumonia

## ANATOMICAL DIAGNOSES

*Choledocholithiasis, with obstruction of common duct*  
*Cholangitis, with formation of small hepatic abscesses*  
Rupture of hepatic abscess into peritoneum  
Subhepatic abscesses  
Biliary cirrhosis  
Jaundice  
Bronchopneumonia, massive  
Operation cholecystectomy, old  
Peritonitis, fibrous, localized  
Adrenocortical adenoma  
Pyelonephritis, acute and chronic.

## PATHOLOGICAL DISCUSSION

DR. MALLORY Autopsy showed a large liver containing multiple abscesses, most of them in the left

lobe and a few in the right, as well as abscesses beneath the liver in both the right and left gutters. There was no general peritonitis. On the left side we were able to trace a communication between one of the hepatic abscesses and the peritoneal abscess. On the right side the communication was not obvious, but I think that it existed. Besides the acute infection in the liver, there was evidence of long-standing disease. The surface of the liver was practically smooth, but the organ was firm and cut with a great deal of difficulty. Microscopical study showed a well developed biliary cirrhosis, which goes with the long-standing history and the biliary obstruction. A stone, 1 cm in diameter, was present in the common duct.

The other findings were a terminal rather extensive bronchopneumonia and markedly enlarged kidneys, which I found rather disappointing histologically. They showed a mild grade of acute and chronic pyelonephritis, and possibly a little tubular swelling and degeneration of the type seen in bile nephrosis but much less than I should expect with a pair of kidneys weighing 500 gm. An incidental microscopical finding of no clinical significance was a large adenoma of the adrenal cortex.

DR. STILLMAN Did the diffuse suppurative cholangitis cause the abscesses?

DR. MALLORY The cholangitis was focal and severe in certain areas, whereas other areas were quite free of it.

DR. STILLMAN Do you think that it was the source of the abscesses?

DR. MALLORY I think that without doubt they were cholangitic abscesses.



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## ALLERGY TO INFLUENZA A AND B VACCINES

THE vaccines that are used for the prophylaxis of virus and rickettsial infections usually consist of suspensions of infected animal tissues in which the virus is either killed or attenuated. These types of vaccines are necessary because of the extreme parasitism of the infectious agents, which have resisted attempts to grow them in mediums that are free of living tissue. In recent years, technics have been developed for the propagation of many viral and rickettsial agents in the tissues or fluid cavities of embryonated hens' eggs. As these technics were perfected, preparations containing the tissues or fluids of infected chick embryos supplanted other types of animal tissues for the preparation of most of these vaccines.

The simplest virus vaccine and the one that is now used most extensively in human beings in this coun-

try is the one containing influenza A and B viruses. Since these viruses grow abundantly in the allantoic fluid of the developed egg, this fluid is the source of the virus that is used for the vaccine. The virus is concentrated by various methods, which involve either adsorption by and elution from embryonic erythrocytes or a similar procedure using other adsorbing agents. Centrifugation and resuspension and, more recently, concentration and purification by means of methyl alcohol have been used in attempts to reduce the amount of egg protein in the final virus suspension.<sup>1</sup> None of these methods have rendered the vaccines entirely free of such protein; however, although the last presumably removes a but an extremely small amount. Formalin is used to inactivate the viruses, and other preservatives are added before the vaccines are released for human use.

The possible effects of injections of influenza virus vaccines in sensitizing the recipients to egg protein and in eliciting allergic reactions in children already sensitive to this protein were summarized recently by Ratner and Untracht.<sup>2</sup> These authors also reviewed the literature on the anaphylactogenic properties of chick-embryo vaccines and recounted the various reports of serious and fatal anaphylactic reactions to injections or reinjections in human beings of vaccines prepared with chick-embryo materials. The results of cutaneous tests for sensitivity to egg proteins and to these vaccines were reviewed, and studies of their own, in which such tests were done with influenza A and B vaccine in a group of 108 allergic children, were reported.

Definite sensitivity to egg white and to vaccine was found in 11 of the patients, but only 5 were regarded as "sensitive enough to warrant circumspection and caution in the use of the vaccine." It was calculated that serious egg allergenicity could be expected in about 1 in every 200 children, and probably somewhat less often in adults. To safeguard the seriously sensitive persons, it is not sufficient to obtain a history of allergy to egg, for often this is vague. A test dose of vaccine should be given before each and every prophylactic injection, and perhaps a test should also be made with egg white. If both or either is strongly positive, the patient is seriously sensitive and vaccine should be

withheld If a systemic reaction results from the test dose, vaccine should be withheld unconditionally

Thirty-nine patients gave only suggestive reactions to one or more of the egg proteins These children were mostly eight to thirteen years of age and were considered to have moderate to mild sensitivity, which at the time was probably not of clinical significance Some of these suggestive reactors were shown to be sensitive to formaldehyde and not to egg

The authors expressed the belief that a history of allergy per se is of no significance, since allergic persons without specific sensitivity to egg protein are no likelier to have a reaction from the vaccine than are nonallergic persons Furthermore, they are of the opinion that a lack of history of sensitivity to egg is of questionable value, since sensitivity was occasionally demonstrated in such persons by skin reactions and even by constitutional reactions to injected egg protein

Ratner and Untracht do not mention the increased danger of reinjection in such cases, a possibility that should be seriously considered The immunity following the injection of influenza vaccines is short-lived, and reinjections at least every two or three years and perhaps again at the first evidence of an outbreak seem to be the only long-range method of effective control with the vaccines now available The danger of such frequent reinjections must be weighed against the possible benefits Two recent developments may help to minimize these dangers The first has already been mentioned—the perfection of vaccines from which most of the protein has been removed<sup>1</sup> The second is the demonstration of antibody responses to single intracutaneous injections of 0.1 cc of vaccine that are similar or superior to those resulting from single subcutaneous injections of 1 cc of the same vaccine.<sup>2</sup> Possibly intracutaneous vaccination will prove effective even with diluted virus, in which case the amount of foreign antigenic protein may be reduced still further and vaccination may then be undertaken repeatedly with safety Only the results of a large and controlled experience will prove whether these possibilities are attainable

A fatal reaction to the injection of influenza vaccine, recently reported by Curphey,<sup>4</sup> serves to illustrate the importance of this problem This followed the subcutaneous injection of 0.5 cc of influenza A and B vaccine in a three-and-a-half-year-old girl The only personal history of allergy was an attack of urticaria ascribed to aspirin The family history was negative, and all members of the family received the same vaccine without reaction The allergic reaction developed four hours after the subcutaneous injection of the vaccine and was characterized by convulsions, abdominal pain, vomiting, hemorrhagic phenomena, hyperthermia and, finally, respiratory arrest and death In discussing this reaction Salk<sup>5</sup> suggests that it was due to the amount of virus given and that such reactions could be avoided by the proper adjustment of the dose given to children

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#### THE BEWILDERED AGE

THERE seems to be a strong tendency, increasing as time goes on, to shape the structure of our lives to that of an inverted pyramid We continue to broaden our activities and our problems of survival in every direction, while still trying to balance on the same uncertain point of contact with the earth The result has been increasing insecurity and instability, reaching down into the lower age groups The American home does not offer all that it should in effort and understanding, and the insecurity of the child may often be a reflection of the insecurity of the parent.

Social, academic and economic pressures have reached too dangerously near a breaking point. Competition has become too keen, and standards have been set too high for many adolescents, who need more and better guidance than they have been getting

This need is recognized by the schools, and recommendations for psychiatric study and treatment are

not infrequently made, but with little apparent realization of the likelihood that in numbers alone the available psychiatric personnel would be entirely inadequate for the job. There is scarcely a person alive of any age who does not occasionally need wise guidance and counsel on matters of personality and social adjustment, but to try and put even a moderate percentage of these into the hands of psychiatrists would at present be impossible.

The need for highly trained and responsibly applied psychiatric help is often grave, and the probability should also be recognized that many of these young persons are failing to receive any form of help because of a technic that lack of man hours and lack of money put beyond their reach. If all the young people who need guidance in human relations are to receive it, less time-consuming and more economical technics are necessary, and a share of the guidance should, if possible, become part of the family obligation.

Guidance in the development of the child's personality should be assumed more frequently than it is now by those who are in the most strategic position to give it because of their acquaintance with the child and who are qualified to add a certain amount of technical knowledge. The specialist should be reserved for the special cases, and guidance should be freely available to the rest from such sources as the family doctor or pediatrician, the pastor and, in many cases, the teacher. The parent should be made a partner in the counsel, not ignored as is too often the case, and the schools themselves, which are so intimately concerned with these difficulties, must be better prepared to help in their solution.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

CLARKE — Joshua W. Clarke, M.D., of Attleboro, died on March 24. He was in his seventy-seventh year.

Dr. Clarke received a medical degree from University of the South, Medical Department, Sewanee, Tennessee, in 1901 and from Medico-Chirurgical College of Philadelphia in 1910. He was chief of obstetrics, Sturdy Memorial Hospital, and was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow, two adopted sons, two stepsons and two sisters survive.

DONOVAN — Thomas R. Donovan, M.D., of Fitchburg, died on March 30. He was in his sixty-fifth year.

Dr. Donovan received his degree from Tufts College Medical School in 1909. He was a member of the staff of the Burbank Hospital and of the New England Obstetrical and Gynecological Society and a fellow of the American College of Surgeons and the American Medical Association.

## MEDICOLEGAL ABSTRACT

### Contempt — and the Doctor's Oath\*

I Swear      by Asclepius, by Hygiea, by Panacea

Of all government's powers, those most important to its successful operation are probably the power to tax and the power to maintain military forces (including the power to conscript). For successful administration of government, on the other hand, the power of eminent domain, usually mentioned in this regard, is probably second to the power to punish individual disobedience of governmental orders (a part of the police power). This latter power is of course exercised in the imposition of sanctions for deviation from the governmental ("public" in a republic or a democracy) policy embodied in the criminal laws, but in a way closer to the dignity and welfare of the government (as distinct from the state operated and administered by it), this power is manifested in the punishments awarded for disregard of individual commands of governmental agencies.

However precisely the criminal laws may be drawn, they cannot hope to anticipate all the situations in which it may become important for an individual to do an act, or to refrain from some act, at the behest of government authority. Some power must exist in the government to support its officials in all those situations, and that power must to be effective be capable of summary application.

The individual's offense against this governmental interest may take the form of a mere overt general disrespect which is most important in the care of agencies and governments whose dignity is of paramount importance, and *lesé majesté* has been, and is still today, a serious offense in governments resting on a strong centralized authority, particularly where that authority is concentrated in one person.<sup>1</sup> In this Country, however, criticism of or disrespect to, the Government or its officials has come to be thought of as a relatively trivial matter. This is particularly true as the attitude has grown in some circles that to be flippant about responsible public officials, to manifest, cleverly, scorn and disrespect for their personal characteristics (if they are of different political philosophies) and to reflect discredit on the traditions they represent, is more than fashionable — it is almost *de rigueur*, it is the countersign of the true intellectual.<sup>2</sup> Only in the case of the courts has the requirement of respect persisted, and flagrant abuses of it are still not tolerated, even today.<sup>3</sup>

Whether the requirement is of the maintenance of a respectful attitude in general or of obedience to a specific order, a violation is classified as a contempt. To indicate the authority of the agency concerned, a contempt may be punished "criminally," by summary action (such punishment not being con-

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sidered a criminal proceeding within the meaning of such Constitutional guaranties as that of trial by jury), or, in a "civil contempt" proceeding, punishment may be ordered conditionally, using it as a threat to induce an obdurate individual to purge himself of his contempt, by recanting, by apology or by obedience to the order previously disregarded.

The governmental power to punish for contempt is widely used by courts of chancery to enforce their decrees, such cases usually involve only civil contempt, a criminal contempt is of course involved if the authority of the chancellor is flouted, but it is usually disregarded unless some act of contempt other than the mere failure or refusal to obey the decree is involved.

Second only in frequency to the chancellor's use of this power, just described, is that of various governmental agencies to compel attendance and truthful testimony by witnesses at various official inquiries, and having discussed the background of the existence of this power, it is my purpose in the remainder of this note to discuss one or two specific problems in its application.<sup>4</sup>

1 It is obvious that facts necessary as a basis for meting out of justice or for establishing legislative policy cannot be obtained where hostility or lack of co-operation is encountered locally, unless the power exists to punish failure or refusal to attend inquiries or to testify. This power is most commonly thought of in connection with judicial bodies<sup>5</sup>, it has been recognized as to courts of chancery since the development of the subpoena in c 1375, and as to common law courts since the *Statute of Elizabeth*<sup>6</sup>. There resides a power in the legislative and executive branches of the government, as well, to summon witnesses to testify, and in the case of the legislature to punish disregard of such summons, but it is not clear that the executive has the latter power. The category of courts possessing the power to punish for contempt includes appellate courts and courts of general jurisdiction, but not inferior courts. A grand jury is, however, an agency whose summons will clearly be enforced by contempt proceedings in the appropriate court, since the grand jury's investigation is one of the basic forms of judicial inquiry by a court of general criminal jurisdiction.

In any case in which the oath may be administered and the question may be asked, if it is answered untruthfully, a criminal penalty for perjury may be imposed, but if the witness refuses to answer the question at all, the criminal law provides for no remedy, in the absence of a statute penalizing mere refusal or failure to answer<sup>7</sup>. In addition, the delays involved in the standard criminal proceeding render it unsatisfactory in a situation where prompt action is required, not to mention the undesirability of a remedy requiring a jury verdict, which cannot be relied on in an area (geographical or legal)

where witnesses are recalcitrant. The summary process of commitment for contempt, not a true criminal proceeding even if criminal contempt is involved, is the device worked out to meet this need, and is admirably designed to impress all concerned with the weight of governmental authority which can be brought to bear when the need arises.

2 In almost perfect balance with the governmental interest in being able to question people and to rely on their answering, and truthfully, is the interest of the individual in not being subjected unjustifiably to official examination (that is, unless there is sufficient necessity to overbalance the inconvenience caused him in the case), and from being subjected to undue pressures to answer questions on matters not the proper concern of the questioning agency.

A basic safeguard of individual interests of this sort is found in the Constitutional prohibitions of cruel and unusual punishments, which means that today fine and imprisonment are the only means which can be employed, with official and public sanction, to make a reluctant witness talk. There are other required procedures to prevent intimidation of witnesses, but the limitations on the types of coercion which may be employed are the most important in this respect.

In addition to these purely procedural safeguards, there are a number of limitations on the things which a witness can be forced by any means to tell the so-called privileges not to testify. Of these the most important category, Constitutionally created, is that against self-incrimination. This privilege is taken for granted today, as having existed from time immemorial, but it did not exist, nor was it thought of, during the centuries of growth of the common law<sup>8</sup>. Both ecclesiastical and royal courts employed the inquisitorial oath, developed under Pope Innocent III in the Thirteenth Century, and though the jurisdiction of the former suffered with the English Reformation under Henry VIII and thereafter, the royal courts did not even thereafter consider such proceedings objectionable because of their origin. It was not until the time of the fall of Charles I that the oath, officially administered to a criminal defendant to require him to testify as to his own guilt, was declared improper (first in *Libburn's Trial*, 1637-1645, and in a number of cases of lesser importance during the same period and shortly afterward), and fell with the Star Chamber Court (a special session of the Privy Council for political cases), its chief remaining employer. Even then, the privilege was limited to the defendant on trial, and was not extended to witnesses not on trial until *Reading's Trial*, in 1679. Under it neither a party nor any other witness in any proceeding, civil or criminal, or in any preliminary official investigation, may over his objection be compelled to give testimony or other evidence which might involve him in criminal liability, as distinct from civil liability,

or from mere public infamy or disgrace. It does not afford protection against disclosure of crimes of others.

Disclosure of information of the affairs of others, to their disadvantage or against their will, is prevented by a different class of privileges, not generally based on Constitutional policy, relating to certain categories of confidential communications. The most important privileged communication of common-law origin, dating back about four centuries, is that between client and attorney. It prevents disclosure by either client or attorney of any confidential information given by the client to the attorney as an attorney, so long as the client may object to such disclosure, but does not apply to information the attorney may obtain from others, or in another capacity than as an attorney.

There are other communications privileged at common law, and some additional privileges created by statute, but most of them affect public or quasi-public officials. One important exception is the privilege applied by common law to private communications between husband and wife, made during the marriage. This privilege, under modern statutes, is generally considered in connection with marital non-waivable disqualifications to testify.

3 Every member of the medical profession considers himself spiritually obligated to at least the substance, in a modern context, of the Hippocratic Oath,<sup>9</sup> pertinent portions of which are as follows:

I swear by Apollo Physician, by Asclepius, by Hygieia, by Panacea, and by all the gods and goddesses, making them my witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad, I will never divulge, holding such things to be holy secrets. Now if I carry out this oath, and break it not, may I gain forever reputation among all men for my life and for my art, but if I transgress it and forswear myself, may the opposite befall me.

Under the policy of this oath, a privilege has been applied to communications between physician and patient, under statutes enacted in many American states, though at common law no privilege attached to private confidences in general, and this rule was applied to confidential communications by patient to physician. There appears to be little logical justification for the privilege, statutory or otherwise, other than the concern of physicians for the honor of their profession — an extralegal consideration, and such statutes have not been passed in Massachusetts or in any other New England state.

The effect of the existence or non-existence of this privilege is easy to see where a case is already in progress, and the physician is called as a witness, but there may be some important collateral effects, even where no case is pending. Suppose the physician learns that a crime has been committed, does he owe the same duty as any other citizen, to notify police authorities, or the prosecuting attorney, or

to testify before a grand jury? Or does he have a limited duty, varying with the seriousness of the crime of which he learns?

Suppose, for example, that the physician learns that a murder or rape has been committed, through his treatment of the only available witness, as a patient. At least under Massachusetts law it is clear that he should notify the authorities that a crime has occurred. But does his duty stop there? May he say to the police "A crime was committed at such and such a time and place. There! Now I've told you, my hands are clean. It's up to you to find out the rest. I know where the evidence is, but I won't tell — physician's oath, you know. The name and address of my patient are confidential. I couldn't tell you *that*?"

The problem would seem to be most clearly presented in the rape example. Not only is that the case in which the physician is most likely to acquire such information, but there, if he does not give full data to the authorities, is the greatest chance for a crime to go unpunished, for in a rape case the *corpus delicti* (in the broad sense) is much less likely to be discovered and recognized without the physician's help.

It seems that in a proper proceeding, before a court, a grand jury or other authorized agency, the physician can be compelled to speak, and is in contempt if he refuses to speak, and may be committed until he does speak. The only remaining question is one of policy, as to how far the court or grand jury should go in exercising the contempt power to further a prosecution or investigation where there has been no complaint.

It may be urged that even though there is no physician-patient privilege in Massachusetts, enough of the policy may be imported from the many states which do have such statutes to grant the physician a little more latitude than a layman in limiting his testimony. This contention suffers, however, in the light of the criticism to which this privilege has been subjected, and it appears difficult to make out a case for even a semi-privilege by decision, where the legislature has not spoken.

The same case may also be considered as depending partly on the public policy of the law of rape. If there remains in the law even vestigially the ancient common-law policy that the whole matter might be cured by a marriage, and that the offense was no felony, but only a misdemeanor, if no complaint was made by the woman injured, then it may be argued, if the woman does not wish to come forward, that the physician is not hindering prosecution of so serious a crime, after all. But if, on the other hand, rape is considered primarily as an offense against the Commonwealth, and if the witness who fails to prosecute is considered as contributing to the threat to other women, which exists so long as the offender is at large, then the silent physician is equally contributing to that same threat to the peace.

of the Commonwealth, and his silence is a serious matter, and it would seem that this is the correct view to take of the matter.<sup>10</sup>

The patient's position in the matter does not justify the physician's refusal to speak. She is not incriminated, unless her failure to complain is treated as making her an accessory, and however logical that might be, it is not a practical consideration. The only interest she can claim in the physician's silence is that of freedom from a distasteful or humiliating contact with the inquiry. But her right of privacy does not extend so far, she has become involved, *volens volens*, in a crime, and owes a citizen's duty to participate in the administration of justice. If the facts are learned by the authorities she can be summoned as a witness, owing the general duty to testify described above. She can even be compelled to undergo physical examination or inspection in open court, to corroborate or discredit her testimony. Her position, then, is such that the physician can not be said to be protecting her legal interests, though it can be appreciated that she may personally desire not to be involved.

What of the physician's professional position? Is he faced with a dilemma, of choice between legal sanctions, if he does not speak, and professional censure, if he does? The answer seems to be that his professional ethics bind him only to remain silent in general conversations, and that compulsory testimony in an official proceeding constitutes no violation of his code of ethics.

There seems to be, then, no private interest, in the case of the physician, sufficient to overbalance the public interest in full and truthful testimony on such serious matters, and since the public interest is paramount in these cases, it seems clear that the power of the court to punish for contempt may properly be exercised in such case, and that the physician may be kept in confinement until he discloses the information which the public interest demands.<sup>11</sup>

## REFERENCES

- 1 Current examples may be found in Latin America and in eastern Europe.
- 2 It is probably unwise to cite specific examples of this attitude; the reader has either observed it personally or he will not believe it in any case.
- 3 Cf. concerning opinions in the recent Supreme Court decision as to John L. Lewis (official citations not available at this writing) *Herald Tribune* (New York) *Boston Herald* March 8 1947 *Time* March 17 1947. A close study of Mr. Lewis' conduct since these proceedings were commenced may prove profitable in an inquiry as to just how much a court will permit in overt manifestations of disrespect without acting today.
- 4 Many readers will of course recognize the relevance of these comments to a recent Superior Court case which gained some newspaper notoriety and was the basis of the *Bulletin's* request to the author to prepare this note.
- 5 It did not always reside in them, but was developed after the ancient concept of the juror as an informed witness was replaced by the modern notion that the juror must be as ignorant as possible (of the case) in order that he may be as impartial an arbiter of matters of fact. Under the older system a witness who was not a juror was something of an interloper, and only during the sixteenth century came to be thought of as essential to the trial of fact. A full discussion of the history of the general testimonial duty is found in *Wigmore on Evidence* (1940) § 2190. Wigmore's work as well as Leach's *Handbook of Massachusetts Evidence* has been drawn on heavily as a source of authority for evidentiary points mentioned herein.

- 6 1562-1563 imposing a penalty and a civil liability for refusal for a witness to attend after summons. That this right belongs not only to the state but also to the individual needing the witness's testimony is shown by Constitutional and statutory guarantees to parties of proofs favorable to them.
- 7 Punishable in Massachusetts under G. L. c. 233 §§ 5 and 11 (apparently under the contempt power recognized by the statutes; no penalty is specified under the latter section for failure to testify as distinct from failure to attend) and c. 277 § 69 (no penalty is specified by this section either).
- 8 This conclusion is drawn from *Wigmore* § 2250 "History of the Privilege (against Self Incrimination)" and the historical sketch which follows is largely condensed from that section.
- 9 *Hippocrates, Works* v. I, p. 299, taken directly from Will Durant, *The Life of Greece* (1939) p. 347.
- 10 Popular feeling on this subject shifts from time to time. It would be interesting to see a study of percentages of convictions in rape cases, before and after the recent Coombes case (*Time*, March 17 1947). Boston newspaper reports, March 1947, and the resulting wave of hysteria as to juvenile delinquency and administration of correction work.
- 11 The witness who gets into trouble for improperly failing to testify even after reading this note, may find solace, or possibly even assistance in the precedent of Miss Beckman as related by Arthur Train.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### POLIOMYELITIS AND TONSILLECTOMY

It has been well established that when poliomyelitis is contracted in the days immediately following the removal of the tonsils and adenoids the involvement of the cord extends higher into the midbrain and the bulbar type of the disease results. This type presents difficult therapeutic and medical-care problems, which, if not adequately met, often lead to a fatal termination.

Recently, in years of high prevalence of poliomyelitis, the Department has issued a warning that elective tonsillectomies should be postponed until incidence of the disease declines to low levels.

Surgeons and hospitals have been inquiring this year regarding the date on which the Department would again issue the warning. Unfortunately the date cannot be determined beforehand. In fact, in some years there has been no good basis for issuing such a warning. For instance, in 1938, 1940 and 1942, when 18, 45 and 36 cases of poliomyelitis were reported respectively for the whole state, no interruption in tonsillectomies was indicated except in a few localized areas. On the other hand, in 1945, with 527 cases, and in 1946, with 379 cases, it seemed wise to suggest postponement.

In most years there is little tendency for poliomyelitis to become relatively prevalent until after August 1. It is a good plan, therefore, to schedule as many elective tonsillectomies as possible before that date, to interfere as little as possible with the program of scheduling necessary operations. After August 1 further operations should be cancelled as soon as it becomes evident that the disease is becoming prevalent in the vicinity of the hospital or of the place of residence of the prospective patient.

## BOOK REVIEWS

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The book is based on a teaching film that shows the methods of examination and the gross motor disturbances in certain diseases of the nervous system Particularly well demonstrated are abnormal involuntary movements, disorders of gait and co-ordination, skilled acts and dysfunction of the muscles supplied by the cranial nerves The illustrations, mostly taken from the film, are excellent, and the book should be of considerable value to medical students and interns In many places the pictures from the basic film are supplemented by diagrams and other illustrations, thus making the book useful by itself The entire 16-mm film may be obtained at a cost of \$450, or a portion covering a separate subject may be purchased

*Modern Management in Clinical Medicine* By F Kenneth Albrecht, M D 4°, cloth, 1238 pp , with 237 illustrations Baltimore Williams and Wilkins Company, 1946 \$10 00

This is a new kind of book on clinical medicine It is intended as a ready reference volume for the doctor's office rather than a textbook for his library The author has succeeded in compiling a large number of medical facts, old and new, obtained from many sources of the vast medical literature He presents to the medical profession—in a condensed and simplified manner—the new advances and technics in the practice of medicine

The first chapter deals with a detailed outline of recording a case history This is followed by an adequate chapter on malnutrition and vitamin-deficiency diseases Then follows the systemic diseases in the usual order The aphorisms on acute appendicitis and the table giving the differential diagnosis of acute abdominal pain, as well as the author's remarks on the pitfalls in the diagnosis of acute abdominal conditions, are excellent Most of what is known about blood dyscrasia is presented in a simplified form in the chapter on diseases of the blood and blood-forming organs This is true of the chapters that follow The author gives not only the essential signs and symptoms in the diagnosis of a certain disease but also the differential diagnosis And what is more important is that treatment is described in detail in each case Of special interest to many a physician at present is the chapter on tropical diseases of postwar importance Nor is the youngest branch of medicine—geriatrics, the care of the aged—forgotten In the chapter on diagnosis and treatment of common skin disorders the author does not mention pemphigus, which is neither rare nor hopeless The book ends with a description of clinical laboratory methods in medicine

The practicing physician will find this volume a valuable companion near his office desk Its twelve hundred pages contain much valuable and practical information, ready at a glance when needed

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(Notices continued on page 70)

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## MEDICAL GROUP PRACTICE IN THE UNITED STATES\*

### I Introduction

G HALSEY HUNT, M.D.†

FOR many years, notably since the report of the Committee on the Costs of Medical Care<sup>1</sup> in 1932, there has been considerable sporadic discussion of group practice, but critical factual analysis of the subject has been meager and limited. World War I apparently acted as a major stimulus for the formation of many medical groups during the immediate post-war years, and there is evidence that a significant expansion of group practice is also following World War II. The responses to the questionnaire submitted by the American Medical Association to medical officers in the armed forces in 1944 indicated that 52 per cent of physicians wished to engage in private group practice after the war.<sup>2</sup> Furthermore, interest in all the technical and social aspects of medical care is at a high pitch, both among the general public and among the professions involved, and shows signs of becoming even intenser. For both these reasons, the time seems ripe to undertake a factual analysis of medical group practice on a scale and of an intensity never before attempted.

### DEFINITIONS

It must be understood at the beginning and kept in mind throughout the discussion that the terms "medical group practice" and "group practice" are generalized, attaining comprehensible and expressible meaning only when they are properly qualified and placed in the appropriate frame of reference. In other words, the unqualified term "group practice" means only that two or more physicians are collaborating to some extent in practicing medicine. As a result, some discussions of group practice include organized hospital staffs and industrial and co-operative medical-care plans, and sometimes even the grouping of several physicians' offices in one building without other organized financial relations. At the other end of the scale, consideration of group practice is sometimes limited to medical organiza-

tions owned by one or more of the practitioners in which all income is pooled and divided among the physicians according to a prearranged formula.

An example of the inclusive definition is provided by Moore,<sup>3</sup> as follows:

It is generally understood that group practice consists of a number of physicians and dentists who combine their professional services, skills and financial resources, to practice the prevention and treatment of disease. These practitioners use common offices facilities and professional equipment. They employ in common, subsidiary personnel for administrative and clinical purposes.

Clark and Clark<sup>4</sup> define the term as "the systematic practice of medicine by groups of physicians working in close professional co-operation and utilizing common equipment and technical personnel."

Roem<sup>5</sup> and the Bureau of Medical Economics of the American Medical Association<sup>6</sup> followed much more restricted definitions in their respective studies. The former defined "private group clinics" by the following characteristic features:

1. Its physicians engaged in co-operative and contiguous medical practice, use many facilities in common, particularly office space, laboratories, and medical equipment.
2. Its physicians — all or most of them — are associated with the clinic on a full time basis.
3. Its services include two or more medical specialties and an attempt is usually made to hold available complete facilities for the patients accepted by the clinic, although some groups avowedly exclude from their services such specialties as obstetrics, ophthalmology, or dentistry.
4. Its patients are the responsibility of the entire group, not merely of individual physicians, although when consultations and special diagnoses are not required, one practitioner may alone treat a given case.
5. Its income is "pooled" and its practitioners have little or no direct financial relationship with patients.
6. Its members determine individual incomes by contract among themselves, rather than directly from their services to patients.
7. Its administration is carried on by a business man rather than a physician, as far as non-medical matters are concerned.
8. Its credit investigations and collection policies are the specialized functions of a business manager rather than the incidental concerns of the several practitioners.

The Bureau of Medical Economics of the American Medical Association included in its 1940 study only the groups with the following characteristics:

\*Published with the permission of the Surgeon General, United States Public Health Service.

†This is the first of a series of reports summarizing the findings of a study of medical group practice initiated by the Division of Public Health Methods, United States Public Health Service, early in 1946.

†Senior Surgeon, United States Public Health Service.



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tion that causes real confusion is the actual time of transition in a given group from the service to the reference category.

### PREVIOUS STUDIES

The literature dealing with the factual aspects of group practice is meager. Rorem<sup>4</sup> studied fifty-five private group clinics for the Committee on the Costs of Medical Care by interviews and mail questionnaires and obtained opinions concerning group practice from ninety-seven physicians in thirty-four clinics and from one hundred and thirty-four physicians in independent practice in twenty-two cities in which group clinics were located. The Bureau of Medical Economics of the American Medical Association published reports in 1933<sup>7</sup> and 1940<sup>8</sup> that summarized the findings of questionnaire studies addressed to secretaries of county medical societies and medical groups. The second of these studies was considerably more extensive than the first, and was reported in a seventy-page pamphlet. Like the other studies cited, it dealt with the number, size and distribution of private medical groups, with their physical facilities and administrative practices and with the opinions of physicians in both group and individual practice. In addition, the report devoted considerable discussion to the historical development of groups and of group practice, correlating the latter to the outrunning by population growth of the medical, hospital and laboratory facilities available in the rapidly growing parts of the country. The report also champions the general practitioner as the only doctor necessary in 85 per cent of all illnesses, questions the value of service groups while stressing the belief that reference groups fulfill an important function adequately and economically and in general holds that, in a medically well developed area, group practice is less effective in providing high quality medical care and in stimulating the professional advancement of the physicians than are general hospitals with organized staffs, independent specialists and well equipped laboratories.

*American Medicine*,<sup>9</sup> published by the American Foundation in 1937 and summarizing narrative replies from two thousand practitioners to a series of questions concerning medical practice, devotes a chapter to group practice. The many comments cited run the gamut of approval and disapproval, but the editor concludes that the weight of opinion is slightly in favor of group practice.

The first efforts to determine the kinds and amounts of medical care furnished by group clinics were made in 1939 and 1940 by Goldmann<sup>10</sup> and by Clark and Clark,<sup>4</sup> who conducted intensive interview studies of seven and fifteen groups respectively. In addition, the Clarks studied samples of the medical records of several groups in an effort to estimate "the degree to which advantage has been taken of the clinic's facilities for diagnosis and

treatment and the extent to which coordination of the various services has been achieved."

Besides these studies there have been many articles by members of groups and by other observers<sup>11-23</sup>. These are of value in conveying the tone and color of group practice, but are for the most part subjective impressions or accounts of personal experiences rather than an impartial evaluation of the general phenomena of group practice. A number of articles have dealt with the fiscal and administrative aspects of the subject, with little consideration of the actual medical practices.<sup>24-34</sup>

### CLAIMS AND CRITICISMS

It may be of value at this point to attempt an enumeration and classification of the chief points on which differences of opinion exist regarding group practice. The warning of the American Medical Association<sup>8</sup> report must be kept in mind throughout this discussion. "It should be evident by this time that generalities in regard to any phase of group practice are dangerous. Nowhere is the opinion of a shrewd French writer more justified than 'No great generalization is ever wholly true—not even this one.'"<sup>35</sup> Few observers of group practice would subscribe without reservation either to the list of advantages cited below or to the list of disadvantages, the nature and ramifications of the subject are such, however, that few observers remain at dead center, balancing advantages and disadvantages evenly. It seems to be a subject on which most students take up a fairly well defined position, for or against, and draw on the rival arsenals of ideas listed below for their verbal ammunition.

The principal advantage claimed for group practice is that modern medicine is so complex that no one physician can comprehend<sup>36</sup> the niceties of diagnosis and treatment, that as a result of this situation, most sick people—if they are to get the best medical care—must be seen by more than one physician and that organization of physicians into groups is the only way in which this can be done efficiently and economically. It is claimed that physicians working together in a group are stimulated to keep up with medical progress more than physicians in individual practice and that each physician, constantly subjected to the informed appraisal of his fellows, has more incentive to do his best work and is less likely to develop slipshod habits of medical practice. The ease and value of consultations is enhanced because the consultant has the patient's whole medical record before him and can more quickly and efficiently bring his own special knowledge to bear on the case. Young physicians, especially those with specialist training, are enabled to concentrate from the beginning on the type of work in which they have been trained, avoiding not only the struggles of establishing a practice but also the loss of skill from disuse that is often the fate of the young specialist. On the

- 1 There must have been at least three physician members
  - 2 The receipts from medical practice must have been pooled in some manner and then redistributed to the members according to some previously arranged plan
  - 3 "Closed staff" hospitals were not included unless the members of the staff pooled the income received for services outside the hospital
  - 4 Purely "diagnostic" groups which receive only referred cases were excluded
  - 5 "Industrial" groups which furnish medical services to a single industry, and thus to only a limited group of the generalized population, were omitted
- Groups that have become notorious for their exaggerated advertising and solicitation, and whose members have, therefore, been excluded from organized medicine, have been omitted from this study

In the absence of a generally accepted definition of group practice, everyone who studies or discusses the subject must set up his own standards and limitations. The present study excludes, tentatively and for the time being, organized hospital staffs in which the physicians participate on a voluntary part-time basis, groups of physicians practicing the same specialty and groups of physicians who, although having contiguous offices and possibly even using secretarial and other personnel on a "shared overhead" basis, have individual financial relations with patients.

The reasoning back of these exclusions may be summarized briefly. Organized hospital staffs, although they may be considered the prototype of group practice, represent a part-time activity from which the physicians do not make their living and that influences only indirectly the major portion of their work. Groups of physicians practicing the same specialty are omitted because they constitute only a quantitative rather than a qualitative increase over the practice of a single person. The third category, comprising what may be called "informal groups," may well be a proper subject for future research but is omitted for the time being, until more is known about the characteristics of the more formally organized groups.

Classification of groups according to sponsorship and type of practice is possibly a more fruitful occupation than attempting to set up an iron-clad definition of group practice. The following are the terms and definitions that are used in the present study.

#### A Classification according to ownership or sponsorship

- 1 *Private groups* Ownership and authority vest in one or more of the physicians who are practicing together as a group
- 2 *Industrial groups* Ownership and authority vest in a commercial company, with the employees of the company as the principal, if not the only, patients
- 3 *Consumer groups* Ownership and authority vest in an organization consisting of potential recipients of medical care. These may be employees of a single company, a consumers' co-

operative, a labor union or a similar organization

4 *Hospital groups* Ownership and authority vest in a nonprofit voluntary community hospital

5 *Medical-school faculty groups* Ownership and authority vest in a university or medical school, or in one of its subsidiaries or components

6 *Government groups* Ownership and authority vest in a federal, state or local governmental agency

#### B Classification according to scope and type of medical services offered

1 *Service groups* Those whose principal activity is the furnishing of complete medical care to a continuing clientele. (This term, although it has been used in previous discussions of group practice, is not altogether satisfactory, since it is not sufficiently descriptive and, in addition, implies falsely that reference groups do not give service. Suggestions for a better term are welcome.)

2 *Reference groups* Those whose principal activity is the furnishing of specialized care to patients referred to them by outside physicians, usually for a single episode of illness, and that ordinarily do not undertake to furnish complete medical care to a continuing clientele.

3 *Diagnostic groups* Reference groups that give little or no treatment.

Even with these broad yet apparently distinctive classifications, ~~several~~ groups possess features that make ~~pro~~ ~~classification~~ difficult. For instance, a group may ~~be~~ ~~composed~~ exclusively of ~~members~~ ~~of a hospital~~ and yet be a ~~private~~ ~~partnership~~ for business ~~with~~ ~~the power~~ ~~to~~ ~~st for clas~~ ~~pointmen~~ ~~pital~~ ~~If the~~ ~~cl~~ ~~intm~~ ~~to~~

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Besides these studies there have been many articles by members of groups and by other observers<sup>11-22</sup>. These are of value in conveying the tone and color of group practice, but are for the most part subjective impressions or accounts of personal experiences rather than an impartial evaluation of the general phenomena of group practice. A number of articles have dealt with the fiscal and administrative aspects of the subject, with little consideration of the actual medical practices.<sup>23-26</sup>

### CLAIMS AND CRITICISMS

It may be of value at this point to attempt an enumeration and classification of the chief points on which differences of opinion exist regarding group practice. The warning of the American Medical Association<sup>4</sup> report must be kept in mind throughout this discussion. "It should be evident by this time that generalities in regard to any phase of group practice are dangerous. Nowhere is the opinion of a shrewd French writer more justified that 'No great generalization is ever wholly true — not even this one.'"<sup>27</sup> Few observers of group practice would subscribe without reservation either to the list of advantages cited below or to the list of disadvantages, the nature and ramifications of the subject are such, however, that few observers remain at dead center, balancing advantages and disadvantages evenly. It seems to be a subject on which most students take up a fairly well defined position, for or against, and draw on the rival arsenals of ideas listed below for their verbal ammunition.

The principal advantage claimed for group practice is that modern medicine is so complex that no one physician can comprehend <sup>28</sup> "the niceties of diagnosis and treatment, that as a result of this situation, most sick people — if they are to get the best medical care — must be seen by more than one physician and that organization of physicians into groups is the only way in which this can be done efficiently and economically." It is claimed that physicians working together in a group are stimulated to keep up with medical progress more than physicians in individual practice and that each physician, constantly subjected to the informed appraisal of his fellows, has more incentive to do his best work and is less likely to develop slipshod habits of medical practice. The ease and value of consultations is enhanced because the consultant has the patient's whole medical record before him and can more quickly and efficiently bring his own special knowledge to bear on the case. Young physicians, especially those with specialist training, are enabled to concentrate from the beginning on the type of work in which they have been trained, avoiding not only the struggles of establishing a practice but also the loss of skill from disuse that is often the fate of the young specialist. On the

financial side a group of men, by pooling their resources, can maintain equipment for diagnosis and treatment that no one of them could maintain individually and can make efficient use of such expensive items as x-ray equipment. Physicians' incomes are more stable, and some claim that they are larger than incomes in individual practice, at least in the early and late years of practice. The physician in a group is freed from direct financial dealings with patients and is therefore able to do his best work medically without worry about whether he will be paid. He is enabled to take vacations and trips for postgraduate study without jeopardizing his practice or his future prospects. The patient benefits by less expensive service (the usual claim is that he gets more service for the same cost than he would get from an individual practitioner), as well as by the ready availability of competent consultation when he needs it. A well run group is alleged to raise the medical standards of the whole community, by exemplifying modern medical care. Groups have the facilities for, and tend to stress, preventive medicine. By providing nursing and secretarial help economically group organization enables the doctor to spend more of his time doing medical work and relieves him of work that can be done as well or better by less highly trained personnel. A final claim is that group practice facilitates the organization and efficient operation of prepayment plans.

Critics of group practice deny some of these advantages categorically but generally take the stand that the advantages are theoretical and that, although they may be true for a few groups, the great majority of groups not only fall far short of the theoretical ideal but also replace alleged advantages with actual faults. The most important criticisms are that most patients can be adequately treated by an individual practitioner with the equipment that any physician would have in his office and that it is inefficient, time consuming and unduly expensive to give every patient the questionable benefit of being treated by two or more physicians in offices fitted out with all the latest diagnostic and therapeutic equipment. This sort of treatment should be reserved for the approximately 15 per cent of patients who really need more than the general practitioner can give them. In addition, the physician in a group is deprived to some extent of independence of judgment and action, and his professional growth is stunted by constant supervision. A physician may get some stimulation from his intimate associations within a group, but he thereby cuts himself off from association with the larger number of physicians in his community, so that he actually suffers a net loss in this respect. The prospect of higher income in group practice is illusory and materializes only for the physician with poor training or personality who could not succeed in individual practice, the well trained physician can

make more in individual practice. (This claim, incidentally, is concurred in by many of the advocates of group practice, who contend that group practice is the best way to practice honest, satisfying medicine, but is not the way to make the most money.) The group's claim for ease of consultation and availability of laboratory service is conceded to be of value in medically undeveloped regions but is said to be of decreasing importance as a region develops specialists, hospitals and laboratories, which enable the practitioner who is not allied with a group to pick the best consultant or laboratory to care for the particular illness of the particular patient, whereas the group physician is limited in his referrals or laboratory work to the available specialists or equipment within the group. Mechanization of medicine, with undue dependence on a dragnet type of laboratory workup, and referral of patients without adequate medical reason are alleged. Allied to these are the allegations that in some groups every patient is "sent through the mill" of referrals and laboratory work, that "made work" is thrown to the less busy members, or that consultations are ordered with an eye on the fee rather than for any medical indication. The obvious advantages of concentration of equipment and the handling of finances by a business manager are often more than counterbalanced by the economic necessity of making the large investment in building and equipment pay its way and by the interjection of business persons untrained in medical ethics into the relations between patient and physician, with the result that unethical promotion and publicity policies often develop. The patient-doctor relation is further disrupted by the fact that a patient does not have "his doctor" who knows and understands him, but has a whole set of physicians, each of whom concerns himself with only a fraction of the patient's person. (Advocates of group practice are somewhat divided regarding the desirability of having a "personal physician" for each patient, but they all agree that such a relation can be maintained in group practice as easily as in individual practice.) The patient's choice of physician, which is ordinarily present in his uncontrolled appointment, is lost as soon as referral becomes necessary, since he is limited to the specialists within the group. Furthermore, many groups that set themselves up as giving complete specialist coverage actually have inadequately trained physicians posing as specialists. This is claimed to apply especially to groups having prepayment plans.

#### ANALYSIS OF CONTROVERSY

These controversial and contradictory sets of statements may be roughly divided into those having to do with medical care per se and those having to do with medical ethics. It will be noted that the former are by implication largely concerned with the practices of service groups. Reference group

receive tacit approval if their specialists are of reasonably adequate caliber and if they avoid unethical practices. The statements that seem to attack group practice as such apply principally to the practices of service groups and with double force to the service groups that have prepayment plans. On the other hand, some of the advantages claimed for group practice also apply to the larger groups with diversified well trained specialists rather than to the small service groups.

It may be said, then, that whereas the fundamental question in group practice concerns its ability to provide medical care, as compared with that afforded by individual practice, realistic consideration of this problem requires that it be broken into two parts—the provision of general medical care and the provision of specialist care. It is essential to determine the extent to which groups carry out each of these functions and to evaluate their success in each case. To what extent does a specific group act as (and replace) a general practitioner, and to what extent is it a specialist? What are the trends in a given group or set of groups—toward increasing reference work or toward a greater volume of general-medical-care work?

Analysis of the controversy from this point of view, and in the light of the preceding paragraphs, shows that the real differences of opinion about group practice center around three basic considerations: whether the great majority (80 to 90 per cent) of sick people suffer from illnesses that can be adequately treated by a well trained general practitioner without consultation, if so, whether it is not wasteful to set up a group organization, with specialists and laboratory equipment, to take care of these ordinary and easily treated illnesses, and whether the 10 to 20 per cent of patients who need specialist care will not receive better care if their physician is free to refer them to the best specialist (or reference group) available for their particular illness, than if he has to refer them to the specialist within his own group, even though better specialists are available outside the group.

Answers to these questions and to such related and subsidiary questions as the role and functions of the individual general practitioner in service groups involve some degree of interpretation and therefore will never be supplied by any simple accumulation of facts, until the questions can be discussed in terms of facts rather than theories and impressions, however, little progress toward their elucidation can be made.

#### PRESENT STUDY

Answers to these basic questions and evaluation of the claimed advantages and disadvantages of group practice must rest on a foundation of factual data that is now lacking. The present study is designed to develop methods by which some of the principal factors peculiar to group practice can be

studied, analyzed and correlated and to apply these methods to a sample of existing groups. An effort will be made to obtain statistical information concerning medical group practice as it is now carried on and to develop statistical indexes of adequacy and quality of medical care. There is at present no way of measuring either of these important components of medical care. They can only be estimated on a subjective basis after prolonged observation by a trained and experienced physician, who is unable to express in exact words all the intangible factors on which he bases his judgment and the relative significance of each. Such subtle and informed judgment cannot be replaced by any purely statistical analysis, but an effort will be made to arrive at indexes that afford a preliminary crude estimate of adequacy and quality. Wherever valid data are available, the kinds and amounts of medical services that groups are called on to furnish will be related to the kinds and amounts of services provided by individual practitioners, and an effort will be made to correlate these data with specific organizational and administrative practices that are peculiar to groups.

#### METHODS

The objectives set for the present study must be sought by a variety of approaches. Determination of the number, size and distribution of groups of various kinds is being attempted by a mail questionnaire. Lists of groups have been obtained through the co-operation of the American Medical Association, Medical Administration Service, Incorporated, and the National Association of Clinic Managers, but none of the available lists include up to date information about the size, type or even the existence of the groups listed. The questionnaire has been circulated to all the groups on these lists, requesting information that will permit their classification according to location, size, ownership or sponsorship, type of practice carried on and type of organization. An effort is also being made to obtain the names of groups that do not appear on the present lists, so that they too may be included in this survey. A questionnaire form (Table 1) has been sent to all groups of which listings were available in 1946. Analyses of the responses will be presented in future studies. Any group that has not received the form is invited to communicate with the author.

For the intensive studies of individual groups, forms have been worked out for obtaining detailed information concerning the personnel of the group, both professional and nonprofessional, its office and equipment facilities, its form of organization, the scope and variety of its medical services, its administrative practices, both medical and business, and its budget by broad categories. The incomes of group members are not included in the study, such a study would be valuable, but present social,

economic and psychologic patterns are such as to rule it out. All this factual information, as well as an opinion survey of members of groups concerning the advantages and disadvantages of group practice and the desirable administrative and professional practices of groups, is obtained by a visit of the study staff to the group being studied, during which

data regarding actual medical practices, including the kinds of illness that groups of various sizes and types are called on to treat, the kinds and amounts of medical services that the groups furnish, the extent to which intragroup consultation is used, the extent to which laboratory and other facilities are utilized and the continuity of care. Such data are

TABLE 1 Questionnaire Sent to All Groups of Which Listings Were Available in 1946

GROUP PRACTICE STUDY	
1	Name of group .....
2	Street address .....
3	City, postal zone state .....
4	Number of physicians practicing (a) exclusively with the group .....
	(do not include interns, residents or fellows) (b) part-time with the group .....
5	Number of dentists practicing (a) exclusively with the group .....
	(b) part-time with the group .....
6	Number of graduate nurses employed by group For out-patient or clinic work .....
	For work in own hospital .....
7	Does the group have its own hospital? Yes.....No..... If yes, number of beds .....
8	Name of medical director, or surgeon-in-chief etc (If none please so state) .....
9	Name of business manager (if none, please so state) .....
	Dr, Mr, Mrs, Miss .....
10	Which of the following statements best characterizes your group
	(a) Informal association of doctors using common facilities (office space laboratory X-ray, etc) to some extent, but not sharing medical responsibility for patients .....
	(b) Formal association of doctors using common facilities .....
	(1) Members share medical responsibility for patients Yes.....No .....
	(2) Form of organization
	(a) Partnership only .....
	(b) Partnership plus employed doctors .....
	If so, number of partners.....
	(c) Single owner plus employed doctors.....
	(d) All doctors employed by sponsoring organization .....
	(e) Other .....
11	Is your organization affiliated with or a part of some other organization (such as a medical school faculty voluntary hospital labor union, consumers cooperative, etc)? Yes.....No .....
	If yes name of organization .....
12	Medical services furnished
	(a) More than one .....(circle fields covered)
	Med Surg Ob Gyn, Ped Eye ENT, X-ray Dentistry
	Other fields (specify) .....
	(b) One specialty only .....Name of specialty.....
13	Primary or principal activity of the group
	(a) Diagnosis only .....
	(b) Consultation or referred service .....
	(c) General medical care .....
14	Does the group itself (or its sponsoring organization) operate a prepayment plan? Yes.....No .....
15	If not, does the group have arrangements to take care of patients for another organization which operates a prepayment plan (medical society plan Blue Shield, cooperative association, etc)? Yes.....No .....
	If yes, name of other organization .....
16	Date of this report .....
17	Name and title of person submitting this report. ....

interviews are carried out with most or all of the physicians, the business staff and the medical-records librarian. One member of the study staff is a physician who attempts a medical evaluation of the general tone of the group, the way in which patients are handled and the surgical and other techniques used.

In addition to the information obtained by these means, the present study is designed to assemble

of basic value in arriving at an estimate of the influence of group organization on medical care and of the desirability of specific practices. To accomplish this, a technic has been worked out for the statistical analysis of samples of the group's medical records. Records of 200 patients seen during a single recent week are selected at random. Each visit of these patients during the week is analyzed according to complaint, physical and laboratory

examination, diagnosis and treatment. In addition, 200 recent patients are followed for two weeks after the first visit, and in each case a summation of the complaint, examination, diagnosis and treatment is obtained. A third part of the record study consists of the analysis of records in 30 recent obstetric cases.

Both major portions of the study — the detailed interviews and the record analysis — need further application before any final conclusions can be drawn concerning their validity in throwing light on some of the controversial points, but the results of their use in five studies to date are encouraging. More detailed reports on the development and form of these study techniques, as well as a preliminary analysis of the findings in the first five studies, will be the subject of future papers.

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## VOLVULUS OF THE CECUM AND ASCENDING COLON\*

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IT IS the purpose of this paper to present 7 cases of volvulus of the cecum and ascending colon and to discuss the preoperative diagnosis of this condition, with emphasis on roentgenologic findings, and the proper surgical treatment.

The problem of volvulus of the cecum is not frequent, and yet one of us (E. L. Y.) has operated on 3 cases in the last four years. The incidence in North America is relatively low. At the Massachusetts General Hospital over a period of fifty-seven years it was 1.15 per cent (6 cases) in 520 cases of acute intestinal obstruction exclusive of those resulting from strangulated external hernia. At the Touro Infirmary, New Orleans, during a sixteen-year period, the incidence was 1.4 per cent (6 cases) in cases of obstruction.<sup>2</sup> It was 0.1 per cent (1 case) in 956 cases of intestinal obstruction from 1934 through 1943 at the Boston City Hospital, and 1.4 per cent (3 cases) in 218 cases at the Faulkner Hospital from 1936 to 1945 inclusive. In spite of this low incidence, it is important to review the subject because early diagnosis will inevitably lower the appalling mortality, which is 100 per cent in unoperated cases<sup>1</sup> and from 17 per cent to 50 per cent in operated cases.<sup>2</sup>

## ETIOLOGY

In the etiology of volvulus of the cecum, acute and chronic types are recognized. Sweet<sup>1</sup> has designated the latter as "subacute, recurring" and states that in both types "there is always a congenital lack of fixation of the cecum with a point of attachment below which the bowel rotates." It will be remembered that in the embryo, during the third stage of intestinal rotation, a process of fusion takes place between the mesentery of the ascending colon and the posterior parietal peritoneum. This process is usually completed by the end of the fifth month, in some cases, however, fusion is incomplete, and the mesentery remains free enough to allow these structures a varying degree of mobility. In a study of anatomic dissections, the cecum in 11.2 per cent of cases was mobile enough to allow the development of volvulus, and reports in the literature suggest that 10 to 15 per cent are free enough to undergo torsion.<sup>3</sup>

With this embryologic fault as a basis, certain extraneous factors may be superimposed to produce twisting of the first part of the large bowel. Miller

and Clagett<sup>4</sup> enumerate these as follows: violent peristalsis following heavy purgation or overeating; abdominal tumors, mesenteric cysts, fecaliths, foreign bodies, direct violence, and habitual constipation. To these may be added acute appendicitis, as evidenced by one of our patients (Case 3), and pregnancy, which may be regarded as a specialized type of abdominal tumor. Basden<sup>5</sup> reported a case of cecal volvulus in a thirty-eight-week-pregnant woman who was thought to be in labor, and Sheldon<sup>6</sup> reported a case in a post-partum patient with onset of symptoms twelve hours after a low forceps delivery.

## DIAGNOSIS

Although the diagnosis of acute volvulus of the cecum is not usually made preoperatively, it is believed that by careful x-ray study and a thorough review of the history and physical findings, it can be arrived at more frequently. The history is one of acute intestinal obstruction, and the essential points are characteristic. About 50 per cent of patients give a history of previous attacks of colicky abdominal pain,<sup>7</sup> as in Case 4 below. The onset is sudden, and the chief complaint is abdominal pain centered in the right lower quadrant. There is usually nausea and vomiting.

The abnormal physical findings, which are confined to the abdomen, consist of distention, generalized tenderness and spasm of the abdominal musculature. On auscultation, peristalsis is obstructive in character or absent in the late cases. The fact that some patients are able to move their bowels or expel flatus does not invalidate the diagnosis.

The laboratory findings are not remarkable. There is usually a moderate leukocytosis. It should be emphasized that a rising white-cell count with a marked shift to the left indicates strangulation of the bowel.

*Roentgenologic Aspects*

In the diagnosis of volvulus of the cecum, the roentgenologist should play an essential role. Despite its rarity, this condition should be included among the differential diagnostic possibilities whenever the scout films customarily taken in acute abdominal emergencies are surveyed. A correct preoperative diagnosis is not only of academic interest but also of great assistance to the surgeon in planning his approach and procedure.

The cardinal points to be remembered are the demonstration of a dilated cecum with variable lengths of dilated ascending colon and terminal

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ileum depending on the type and extent of the congenital mesenteric attachment, an abnormal position of the dilated cecum, which is found in the left upper quadrant in over 90 per cent of cases, together with the absence of a normal appearing cecal outline in the right lower quadrant — previous films showing its normal position or mobilization are helpful but not always available, the demonstration, by barium-enema examination, that the dilated portion of large bowel is proximal to the point of obstruction of the barium column, no barium-outlined cecum being identified in the right lower quadrant, and, also by barium-enema examination, the observation of at least the initial twisting and torsion of the mucosal pattern outlined by barium, bowel wall and gas

### DIFFERENTIAL DIAGNOSIS

**Obstructing tumors** The twisting mucosal pattern is typical of volvulus, not of tumor, and the abnormal position of the cecum should help in the differentiation. In one of the cases reported below (Case 5) these conditions co-existed.

**Obstructing adhesions** Again, the abnormal position of the cecum and the characteristic mucosal twisting should aid in the differential diagnosis. In one case reported below (Case 6) there were volvulus and adhesions.

**Dilated obstructed stomach** Confusion may arise from the position of the gas-filled cecum in the left upper quadrant, which shows a large fluid level in films made in the erect position. Some authors have solved this problem by intubating the stomach or outlining it with a swallow of barium and separating the cecum from the stomach by fluoroscopy or films, as in Case 7 reported below.

**Redundancy of the colon** In Case 6, due to a redundant bowel, the point of arrest of the barium column simulated a small, normally placed cecum low in the right lower quadrant. Further study of the films showed the early torsion of the mucosa in the volvulus and a dilated cecum in the left upper quadrant.

### TREATMENT

The treatment of acute cecal volvulus is surgical, and it is obvious that the earlier these patients are subjected to surgery the better the results, for the longer the blood supply has been compromised the more radical the necessary surgery must be. The fact that numerous technical procedures have been recommended suggests that the results of surgery have not been too satisfactory in the past.

There are several points to be kept in mind concerning the management of acute volvulus. The volvulus must be reduced, the obstruction must be relieved, and one must attempt to prevent recurrence. The various methods of accomplishing these ends are as follows: detorsion and cecostomy, which result in fixation of the cecum to the anterior wall,

decompressing the bowel at the same time, detorsion and cecocolic plication and fixation, and detorsion and resection of the cecum and ascending colon. Simple untwisting of the volvulus is never permissible.

It should be pointed out that there is no one set of rules that supersedes surgical judgment. For example, to return a distended, thin-walled, malnourished cecum to its normal position after cecostomy is to invite trouble. The patient in a case reported in the literature died on the tenth day after this procedure, and autopsy demonstrated that the cecostomy was tight but that peritonitis had developed, apparently from the passage of contaminated material through a thin, distended bowel wall.<sup>2</sup>

The same conditions prevail regarding resection of the volvulus followed by primary ileotransverse colostomy. One case (Case 5) in this series and another recorded by Holman<sup>8</sup> demonstrate the danger of this maneuver. Death occurred on the ninth and seventh postoperative days, respectively, and although no autopsies were performed, it may be inferred that failure of the primary suture of a distended, edematous bowel wall was the cause.

As pointed out below, the procedure of choice when there is the slightest question of the competency of the ascending colon is reduction of the volvulus, and resection of the cecum and ascending colon by the method of Mikulicz. Since most patients are extremely ill, careful attention must be given to their postoperative care to ensure proper fluid and electrolyte balance and adequate nutrition.

### CASE REPORTS

**CASE 1.\*** A 47-year-old woman was admitted to the hospital on January 19, 1936, with a chief complaint of abdominal pain of 6 hours' duration. She had been awakened from a sound sleep by the pain, which was sharp constant and generalized throughout the abdomen. Shortly after the onset of symptoms, she took a dose of Agarol and later had two normal bowel movements. The pain persisted and she was sent to the hospital. No mention of vomiting was made.

The past history was irrelevant. The patient's general health has been good.

There were no remarkable physical findings except in the abdomen, where a peculiar form of distention was noted. It was somewhat sausage shaped and extended from the left upper quadrant to the right lower quadrant. There was no spasm of the abdominal muscles. The point of maximum tenderness was in the right upper quadrant. Vaginal and rectal examinations were negative.

The blood pressure was 120/70.

Examination of the blood revealed a white-cell count of 16,000. The urine showed a trace of albumin, and the sediment contained 2 to 4 white cells and 3 to 5 red cells per high power field.

No preoperative x-ray films were taken.

When the abdomen was opened through a right para median incision there was an escape of cloudy fluid. Exploration revealed the cecum and the ascending colon to be rotated twice on the long axis in a clockwise direction. The cecum lay to the left of the midline above the umbilicus and was discolored. The mesentery measured 15 cm in length. After the volvulus had been reduced the bowel did

\*Reported through the courtesy of Dr. Charles C. Ludd, of the Boston City Hospital.

not return to normal color, and accordingly a double barrel colostomy was done between the proximal end of the transverse colon and the terminal ileum, the cecum and ascending colon being removed. The immediate postoperative condition was fair.

Five days later a clamp was applied to crush the spur, and 43 days after the original operation, the colostomy was closed. There was a stormy postoperative course, during which the patient developed lobar pneumonia. She recovered, however,

Rectal examination was negative.

The blood pressure was 155/90.

Examination of the blood showed a white-cell count of 24,000 with slight shift to the left.

X-ray examination by Dr. Alexander Vance was reported as follows:

Plain films of the abdomen show a huge gas shadow under the left diaphragm extending across to the right of

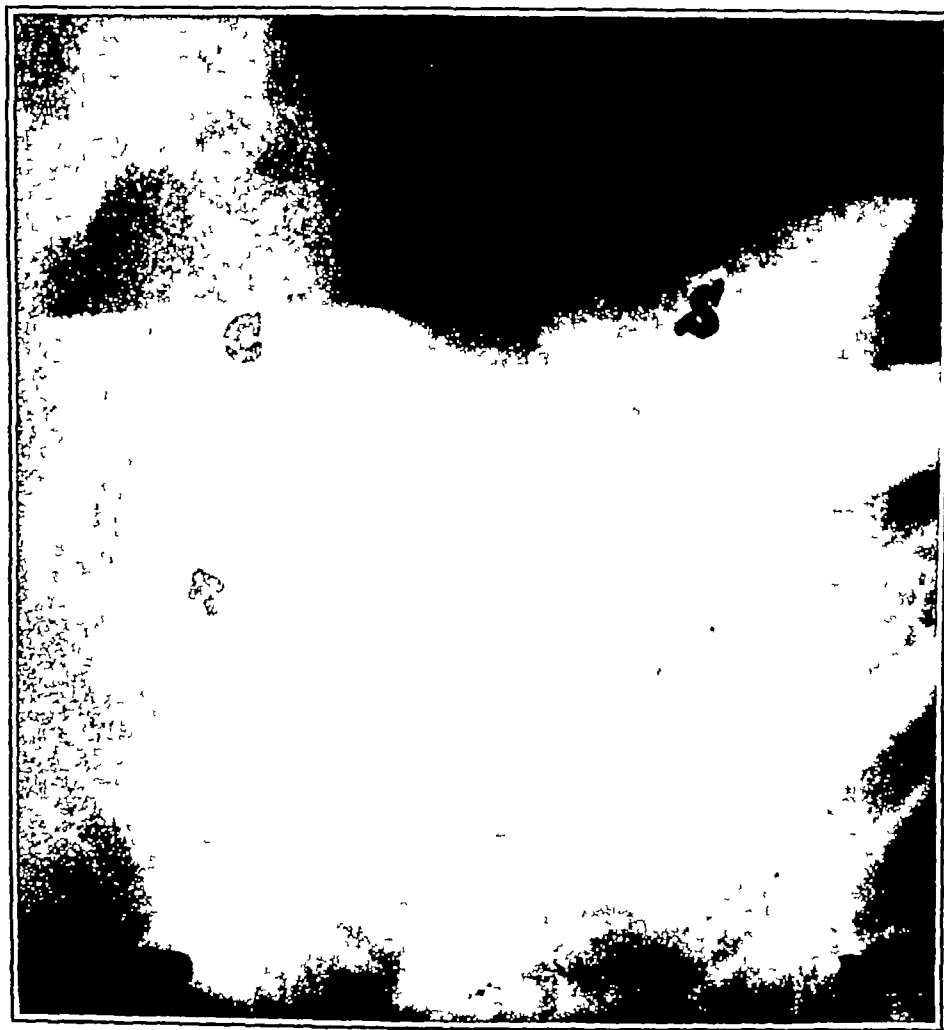


FIGURE 1 Case 2

*A barium enema demonstrates the point of torsion of the volvulus at the arrow "S". "C" is barium in the stomach. "C" is the fluid level in the dilated cecum, with gas above it extending into the left upper quadrant.*

and was discharged well from the hospital 93 days after admission.

**CASE 2\*** A 54-year-old man was admitted to the hospital on June 11, 1941, with a chief complaint of swelling and distress in the epigastrium of 3 weeks' duration. The symptoms had gradually increased during the week prior to admission. There was no nausea or vomiting. The bowels had moved daily until the 3rd week of symptoms.

The past history was irrelevant.

Physical examination was negative. The abdomen was markedly enlarged and tense, with distention most noticeable above the umbilicus. Peristalsis was normal in the lower third of the abdomen. An ovoid mass, 22 cm in diameter, was roughly outlined in the right upper abdomen. There was no abdominal tenderness.

\*Reported through the courtesy of Drs. John Marshall, Walter Garrey and Alexander Vance of the United States Naval Hospital, Chelsea, Massachusetts.

the midline. There are no other dilated loops of bowel. The area of the cecum is clear, and no small bowel is outlined by gas shadows. A swallow of barium given by mouth demonstrates the stomach to be posterior and displaced slightly by the extremely large gas-filled mass.

A barium enema was administered, and the barium flowed freely to the middle portion of the ascending colon, beyond which barium failed to pass. The tip of the obstructed area was pointed, suggesting volvulus (Fig 1). The findings were those of a hugely dilated cecum, with volvulus, probably on the basis of incomplete rotation and a long mesentery.

The abdomen was opened through a right rectus incision, and a distended large bowel presented. This was decompressed with a needle puncture followed by purse-string suture. A volvulus of the cecum and right colon was then demonstrated. This was reduced, and a Mikulicz ileotrans-

verse colostomy was performed. The immediate postoperative condition was satisfactory.

The patient had a moderately stormy course, apparently owing to an attack of bronchopneumonia. He was well enough, however, to have the spur crushed 13 days after the original operation. The colostomy was closed 85 days after admission. The patient had an uneventful recovery and was discharged 105 days after admission.

**CASE 3** A 14-year-old boy was admitted to the hospital on November 23, 1942, with the chief complaint of pain

Examination of the blood disclosed a white-cell count of 8100 with 87 per cent neutrophils. The urine was normal except for 4 to 6 white cells per high power field in the sediment.

No preoperative x-ray films were taken.

When the abdomen was opened through a right rectus muscle retracting incision the cecum and appendix could not be felt. Exploration revealed a balloon-like mass in the pelvis which was found to be a much dilated and congested cecum with the ileum entering the lateral side of the mass. The cecum and ascending colon were twisted 145

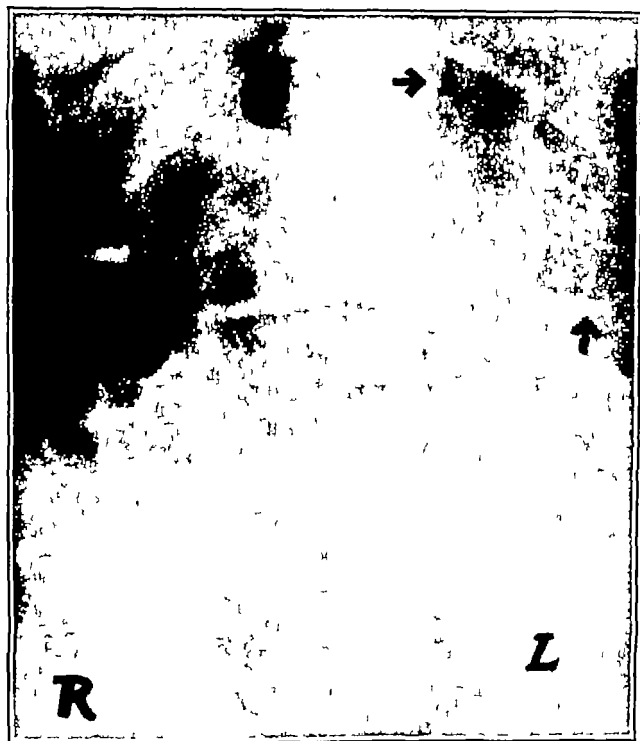


FIGURE 2 Case 4

*This scout film demonstrates the dilated cecum in the left upper quadrant. It should be noted that the cecal shadow is absent in the right lower quadrant.*

in the right lower quadrant of 4 hours duration. One week prior to admission he had experienced epigastric pain and nausea. The family physician started him on an ulcer regime but the symptoms persisted intermittently throughout the week. The patient vomited once during an attack. During this period the bowels did not move except on the day before admission following an enema.

The past history was irrelevant.

Physical examination was negative except for the abdomen. There was no distention but there was marked tenderness in the right lower quadrant with some increased muscle tone over the entire abdomen. On rectal examination there was marked tenderness in the right lower quadrant but no masses were felt. The blood pressure was 130/70

times on the long axis and there was no mesentery to the first 15 cm of the large bowel. There was no evidence of gangrene and accordingly the volvulus was reduced and the appendix removed although it looked grossly normal. The cecum was emptied of gas, plicated and fixed in the iliac fossa.

The pathological diagnosis was acute appendicitis.

The patient made an uneventful recovery and was discharged 13 days after admission.

**CASE 4** A 53-year-old man was admitted to the hospital on March 27, 1943, with a chief complaint of pain in the right upper quadrant of 24 hours duration. A renal calculus had been removed in June 1942, and 5 weeks after discharge



B

A

FIGURE 3 Case 4  
 A is a full barium-enema film demonstrating arrest of the barium column with torsion of the colon at that point. In B, a spot film, the site of torsion of the volvulus is outlined by barium, bowel wall and gas, with twisting of the mucosal relief.



FIGURE 4. Case 6

A is a full barium-enema film demonstrating the obstruction, with twisting of the volvulus outlined by a thin streak of barium above the arrow. Note the redundant colon and the point of barium arrest lying in the right lower quadrant and simulating the cecum. B is an evacuation film showing the lortion of the volvulus at the arrow. The dilated cecum is well seen in the left upper quadrant.

became disoriented and weakened and died on the 9th post-operative day. No autopsy was performed.

**CASE 6** A 59-year-old woman was admitted to the hospital on November 24, 1945, with a chief complaint of nausea and vomiting of 5 days' duration. She had been constipated for 4 months. Four days before admission, she had become nauseated, but she had not vomited until 2 days later after a large meal that she had forced herself to eat. An enema at that time was returned clear, although the bowels had not moved for 2 days.

A pelvic laparotomy had been performed in 1910, and lysis of adhesions for intestinal obstruction in 1930.

Physical examination was negative except for the abdomen, which was distended throughout, with hyperperistalsis.

Examination of the blood disclosed a hemoglobin of 13.4 gm and a white-cell count of 16,600, with 70 per cent neutrophils. The urine was normal.

A previous barium-enema examination, done on September 26, 1930, had shown a normal position of the colon. A scout film of the abdomen 1 day after admission revealed dilatation of a loop of large bowel in the left upper quadrant, with numerous loops of dilated small bowel. At examination on the next day the barium column flowed freely through the colon, which had numerous redundant loops. The splenic flexure was above the gas-distended cecum in the left upper quadrant. Barium passed readily to the right iliac fossa, where the column met arrest. The point of torsion appeared to be pulled across toward the midline, and there was a twisting of the mucosal relief at the point of arrest typical of volvulus (Fig 4).

At operation numerous angulations of small bowel from adhesions were encountered. The cecum and ascending colon had rotated twice on its mesentery and had included loops of small bowel in the volvulus. The mass lay at the splenic flexure. Because of the marked redundancy a Mikulicz resection was done. The immediate postoperative condition was good.

On December 2 the patient showed signs of small-bowel obstruction. She was treated supportively with constant Wangenstein suction and parenteral therapy, without operative interference. The colostomy closed on January 9. Following this an abscess developed on the buttocks that was incised and drained. The patient was discharged well and with normal bowel function 67 days after admission.

**CASE 7\*** A 70-year-old woman was admitted to the hospital on December 1, 1945, with the chief complaint of colicky pain in the abdomen of 2 days' duration. The pain subsided shortly after onset, but the night before admission it became severe and generalized throughout the abdomen. The patient had not expelled flatus or moved the bowels since the onset of symptoms. She had had two similar but milder episodes during the previous year.

A subtotal gastric resection had been performed in 1944 for an ulcer in the prepyloric region of the stomach.

Physical examination was essentially negative. The abdomen was distended, and there was generalized tenderness throughout. Peristalsis was hyperactive.

A barium-enema examination 1 year previously had shown incomplete rotation of the cecum. A scout film on admission demonstrated a dilated cecum in the left upper quadrant (Fig 5). The x-ray diagnosis by Dr Stanley Wilson was volvulus of the cecum.

At operation the dilated cecum was found in the left upper quadrant. The blood supply had not been compromised, and the volvulus was accordingly reduced and a cecostomy performed.

The patient made an uneventful recovery and was discharged from the hospital 22 days after admission.

### SUMMARY

The incidence, etiology, diagnosis and treatment of volvulus of the cecum and ascending colon are discussed. It is emphasized that treatment is surgical and that if there is the slightest question of the

viability of the cecum, a Mikulicz resection and exteriorization should be done. Cecocolic fixation and plication with cecostomy may be employed when the bowel has not been damaged.

If cecal volvulus is included in the differential possibilities when scout films are taken in acute abdominal conditions, the preoperative diagnosis can be established roentgenologically. Confirmation is assured by barium-enema examination.

From the scout films, the abnormally placed and locally dilated portions of large bowel should be identified as cecum, particularly in view of an absent cecal outline in the right lower quadrant. The barium enema corroborates these observations and demonstrates the twisting and torsion of the mucosal pattern at the point of barium arrest, characteristic of volvulus.

Seven cases are reported. Although no statistical conclusions can be drawn from this series, some of the notable features are as follows: all but 1 of the patients were in the middle or elderly age groups, 2 patients had had more than one previous attack, 4 patients were able to expel flatus or move the bowels in spite of the volvulus, at operation the most frequent location of the cecum was the left upper quadrant, and the only death occurred in a case treated by resection and primary ileotransverse colostomy. This is in accord with similar cases reported in the literature.

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\*Reported through the courtesy of Drs. Claude E. Welch, of the Massachusetts General Hospital, and Stanley Wilson, of Salem.

## CARCINOMA OF THE ISLETS OF LANGERHANS WITH HYPERINSULINISM\*

## Report of a Case

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THREE years after the isolation of insulin by Banting and Best<sup>1</sup> in 1921, Harris<sup>2</sup> formulated the concept of hyperinsulinism. In 1927 Wilder<sup>3</sup> reported the first recognized case. Since then over 150 cases of benign insulin-producing tumor have been reported. Unequivocal cases of carcinoma of the islets of Langerhans are unusual, we have been able to collect 23 such cases from the literature.<sup>4-10</sup> In 16 of these, hypoglycemia was observed. The following case is believed to represent another example of carcinoma of the islets of Langerhans causing hypoglycemia.

H S, a 40-year-old man was sent to a hospital in July 1945, by his physician, who had found a mass in the right

upper quadrant. For the preceding month he had noted urinary frequency.

Physical examination at that time showed a poorly developed undernourished man with a tender nodular liver whose edge was palpable four fingerbreadths below the right costal margin. There were no other significant findings. Roentgenograms of the entire gastrointestinal tract were normal. Three separate determinations of the fasting blood glucose gave values of 67, 72 and 89 mg per 100 cc. Other laboratory data are not available. The patient was discharged on September 26, with a diagnosis of possible portal cirrhosis or carcinoma of the liver.

Thereafter the patient, according to his wife, continued to suffer abdominal pain and complained of feeling constantly weak and tired. His wife who was with him most of the time never noted any cold sweats, episodes of severe hunger, sudden mental changes, diplopia, sudden tremors, twitchings,

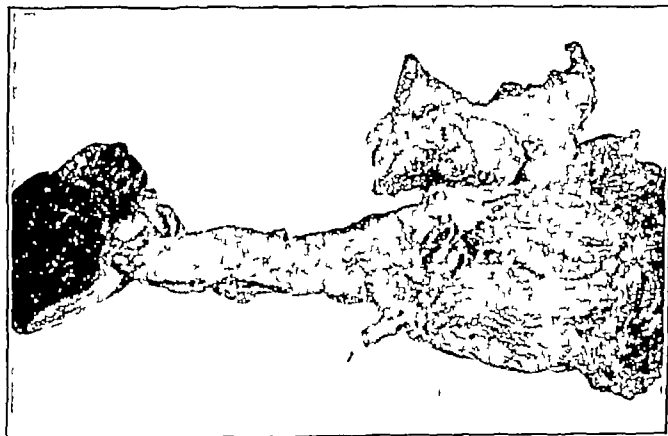


FIGURE 1 Longitudinal Section of Pancreas and Adjacent Organs

The primary tumor site can be made out in the tail of the pancreas. To the right a portion of the gastric wall is seen in relation to a large mass of tumor tissue.

upper quadrant. At that time the patient gave a history of a weight loss of 27 pounds in 2 months. For 6 weeks before admission epigastric pain beginning about 1 hour before and ending approximately 2 hours after meals had troubled the patient, but except for a 2-day period of vomiting and diarrhea 3 or 4 weeks before admission he denied other gastrointestinal symptoms. Amphojel and mineral oil had relieved the pain somewhat. He admitted that he habitually

somnolence or loss of consciousness. He seemed despondent however much of the time.

On October 20 the patient was admitted to this hospital in deep coma. He had apparently lapsed into coma while alone for a few hours at home.

Physical examination showed an emaciated man with sparse axillary and pubic hair. The skin was cold and moist and there was an early decubitus ulcer over the sacrum. The liver whose edge was blunt and extended four or five fingerbreadths below the right costal margin was hard; most examiners believed that definite nodules could be made out. A firm epigastric mass was palpated; this might have

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been a large nodule in the liver or a separate mass. The rest of the examination was not remarkable.

The temperature was 98.2°F by rectum, the respirations 20 and deep, and the pulse 100 and regular. The blood pressure was 150/90.

The blood glucose was 11 mg and the blood urea 10 mg per 100 cc. Later, examination of the blood revealed a red-cell count of 3,510,000, with a hemoglobin of 10 gm per 100 cc and a blood cholesterol of 104 mg per 100 cc, a blood Hinton test was negative.

About 100 cc of watery fluid was aspirated from the stomach, and 50 cc of 50 per cent glucose was administered

urinary output, which had been over 2800 cc in the first 24 hours, began to decrease sharply.

Thirty-four hours after admission the temperature rose to 102°F by rectum, and the respirations increased to 36 per minute. There were medium moist rales and bronchial breath sounds in the left lung anteriorly and at the left base. The white-cell count was 21,000, 30,000 units of penicillin was given intramuscularly at that time, followed by 20,000 units every 2 hours. During the next 8 hours the patient became virtually anuric. The blood pressure, which had varied between 100/60 and 150/80, fell to 66/60, and the skin became cold and moist. Thirty-eight hours after admission

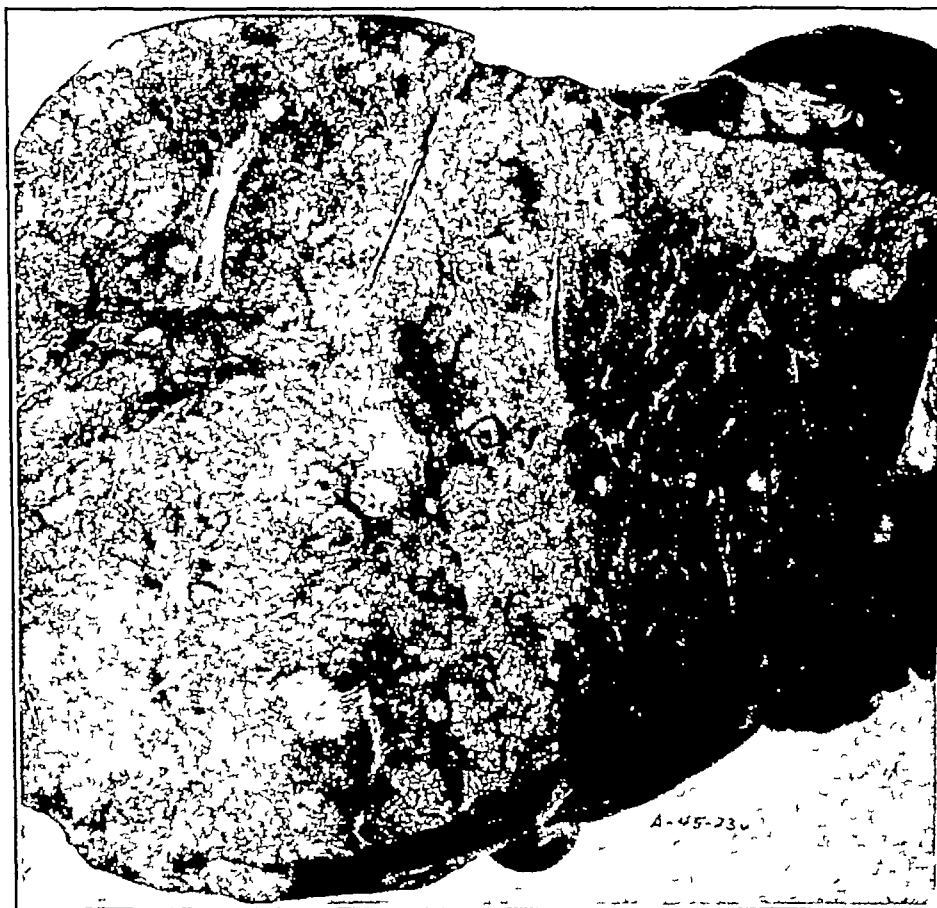


FIGURE 2 Section of the Liver, Showing Massive Metastases.

intravenously, within less than 1 minute the patient recovered consciousness completely and was able to converse rationally, although he could not remember what had happened to him. Since vomiting followed every attempt to give food by mouth, further glucose was administered, most of it intravenously and the rest subcutaneously. Crude liver extract and supplementary vitamins were also injected parenterally. Several urine specimens showed a positive Benedict's test, which never exceeded a green reaction. Acetonuria was never present.

It was the opinion of both the Medical and Surgical services that the hypoglycemia was most probably due to an islet-cell tumor, and an additional diagnosis of portal cirrhosis was made. Opinion was divided regarding whether there were metastatic nodules in the liver, but it was agreed that the patient should be given the benefit of the doubt and explored in the hope that the tumor might be benign. The use of alloxan was suggested in the event that surgical treatment should prove impossible.

The patient's condition would not tolerate surgery at that time, however. To the general picture of cachexia there was added abdominal distention, with epigastric spasm on occasions, severe abdominal pain necessitated opiates. The

the blood urea nitrogen was 7 mg., and the sodium chloride 436 mg per 100 cc.

Plasma was administered intravenously. The blood pressure rose thereafter but did not go above 90/60 during the rest of the hospital course despite further plasma. Moderate cyanosis developed, oxygen was given by Burgess box.

Although the patient's inability to go without nourishment long enough to reach an adequate fasting blood sugar level made a standard glucose-tolerance test inadvisable, the rapidity with which glucose disappeared from the blood with little concomitant glycosuria pointed emphatically to hyperinsulinism. To show this to greater advantage the patient was given 210 gm of glucose intravenously (in 5 per cent and 15 per cent solutions) from the 42nd to the 50th hour after admission. During that time 500 cc of a 5 per cent glucose solution was also injected subcutaneously. All glucose intake was then discontinued abruptly. The blood sugar was 43, 23 and 24 mg per 100 cc, respectively, 30, 60 and 90 minutes later. By that time the neurologic signs precluded further starvation, 50 cc of 50 per cent glucose administered intravenously temporarily restored the blood sugar.

Since it did not seem possible that the patient would improve sufficiently to permit surgical intervention, arrange-

ments to procure alloxan were made with the Department of Biology of Brown University. Alloxan administration was to be started on the following day.

Abdominal pain continued to be severe, and the patient vomited frequently. The urine output was only 1 or 2 cc per hour. The urine contained many red and white cells and granular casts. There was never more than a trace of sugar present. The temperature ranged between 100 and 102°F.

While glucose and physiologic saline solutions were given parenterally, an attempt was made to stabilize the blood glucose by furnishing protein. The patient received a 5 per cent solution of amino acids along with part of the parenteral glucose, 50 gm of protein was given in this way. A total of 1000 cc of plasma was administered during the patient's stay in the hospital. From the 53rd to the 65th hour after admission while parenteral glucose, sodium chloride and protein were given as noted above, whole adrenocortical extract (Eschatin) was given subcutaneously. The blood glucose preceding the first dose was 155 mg per 100 cc. Four hours after the administration of 10 cc, the blood glucose was 189 mg per 100 cc. A second dose of 5 cc was administered and 1 hour later the blood glucose was 173 mg per 100 cc. Two more 5-cc doses were given 8 and 12 hours after the initial dose. The blood glucose after the latter dose was 1800 mg per 100 cc. At that time the blood sodium chloride

tingly with the normal pancreas infiltrating in the form of thin bands and blunt projections. The head and body of the pancreas were normal. In the region of the gastrohepatic ligament there was a roughly spherical mass (10 by 6 by 8 cm) of whitish-gray tissue with frequent, soft, pinkish gray areas. The peritoneum in this area was studded with friable nodules of similar tissue that merged with the main mass and enlarged lymph nodes which were also involved. The liver weighed 3500 gm, its surface was extensively mottled by areas of pinkish-gray tissue. On section this tissue was



FIGURE 3 Section of the Primary Tumor in the Pancreas

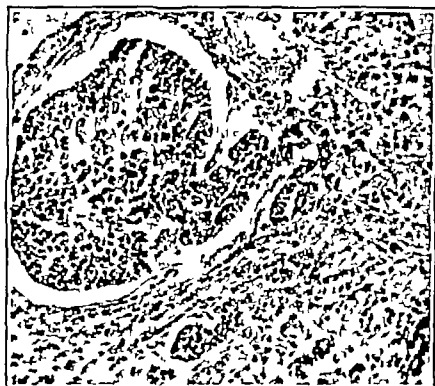


FIGURE 4 Section of the Metastatic Tumor in the Liver

found to have supplanted a large portion of the liver parenchyma. The right lobe was almost totally replaced by tumor tissue and the left lobe was involved to a lesser degree. All in all approximately  $\frac{3}{4}$  of the liver had been supplanted by tumor (Fig 2). The adrenal glands, kidneys and bladder were normal.

The tumor in the pancreas was composed of oval or polyhedral cells. The cytoplasm was slightly acidophilic and fairly abundant. The nuclei were well stained, round and centrally placed in the cells, which were quite uniform in size and shape. Infrequent mitoses were noted. The cells were arranged in solid groups in the form of short anastomosing cords and rounded collections which at times attained considerable size. Occasionally these collections of cells were lined by a clear space and were in intimate contact with fine-walled capillaries. It was difficult to distinguish these structures from normal islets. At other points the cells were gathered in smaller round groups, separated from each other by thin strands of connective tissue with abundant capillaries (Fig 3). They tended to be larger than the usual islets of Langerhans. In no area did the tumor simulate acinus or duct formation. Throughout the tumor large areas of necrosis and hyalinization were noted. Thick connective-tissue trabeculations crossed through the neoplasm, separating the tumor into irregular nodules. No evidence of capsulation was present, and neoplastic cells were seen invading the normal pancreas irregularly. The uninvolved portions of the pancreas presented a normal pattern; the islets were not remarkable. In the liver (Fig 4) and lymph nodes the tumor adopted essentially the same structure and cytology. Small nodules of tumor tissue were well preserved, otherwise there was considerable necrosis. The liver-cell cords were well preserved. In the neighborhood of metastases however, there was some vacuolization of cells and disintegration. Efforts to stain the tumor specifically with Mallory's modified Azan stain and the Gomori's phloxine stain gave negative results.

We are indebted to Dr. George Gomori, who of the tissue

was 404 mg, the urea nitrogen 30 mg and the creatinine 4.3 mg per 100 cc. The white-cell count was 14,500 with 50 per cent mature and 33 per cent young neutrophils, 11 per cent myelocytes, 4 per cent lymphocytes and 2 per cent monocytes.

Following this the patient received intravenous physiologic saline solution and plasma, the dosage schedule of adrenocortical extract continuing as before. No improvement occurred and the patient expired 72 hours after admission. In a blood specimen taken 2 hours post mortem the sodium chloride was 476 mg, and the glucose 110 mg per 100 cc, and the icteric index was reported as less than 6 units.

The total carbohydrate intake was 1680 gm, the total protein intake 110 gm, and the total sodium chloride intake approximately 32 gm—excluding the small amount of nourishment that the patient was able to take by mouth.

**Autopsy.** Post mortem examination was performed 2 hours after death, permission being restricted to the abdomen. Positive findings included the distal 6 cm of the tail of the pancreas, which was occupied by an elevated grayish white, firm tissue. The surface was moderately lobulated and smooth. The tip of the pancreas was adherent to the hilus of the spleen and the capsule of the spleen had been infiltrated superficially (Fig 1). On section this tissue blended indis-

The kidneys showed congestion throughout. Minute vacuoles were noted in the cells of the proximal convoluted tubules. Rare casts were seen. Otherwise, there was nothing abnormal. Sections stained for glycogen degeneration revealed no abnormality.

Multiple sections through the adrenal glands demonstrated abundant normal adrenal tissue.

After preservation in the icebox for 17 hours, approximately 25 gm of tissue taken from many portions of the liver metastases was extracted according to the method of Best, Jephcott and Scott.<sup>27</sup> A rabbit weighing 2 kilograms

any surgical procedure doubtful, the best interests of the patient demanded that he receive the benefit of exploration, provided that his condition could be sufficiently improved to tolerate the operation. It is unfortunate that alloxan was not immediately available. The experience of Brunshwig et al<sup>24, 25</sup> in a case of hyperinsulinism due to malignant islet-cell tumor suggests that the use of alloxan is of

TABLE 1 *Clinical and Pathological Data in 23 Cases of Islet-Cell Carcinoma Reported in the Literature*

AUTHOR	YEAR	AGE OF PATIENT	SEX	TOTAL DURATION OF SYMPTOMS	SITE	HYPOGLYCEMIA	INSULIN EFFECT OF TUMOR	ONSET OF HYPOGLYCEMIA	LOCATION OF METASTASES
Zanetti <sup>4</sup>	1927	56	M	No data	Whole pancreas	Not mentioned	Not tested	—	Stomach, liver, and lymph nodes
Wilder et al. <sup>5</sup>	1927	40	M	21 mo	Tail	Present	Present	Gradual	Liver and lymph nodes
Hamdi <sup>6</sup>	1932	52	M	No data	Tail	Not mentioned	Not tested	—	Stomach
Judd et al. <sup>7</sup>	1934	18	F	14 mo	Whole pancreas	Present	Not tested	Gradual	Liver (no autopsy performed)
Jacobsen <sup>8</sup>	1934	36	M	12 to 18 mo	Head	Present	Not tested	Sudden	Liver
Bickel et al. <sup>9</sup>	1935	56	M	10 mo	Body and tail	Present	Present	Gradual	Generalized
Evangelisti <sup>10</sup>	1935	65	M	No data	Body and tail	Not mentioned	Not tested	—	Liver and omentum
Cragg et al. <sup>11</sup>	1937	41	F	7 mo	Whole pancreas	Present	Present	Gradual	Liver and lymph nodes
Joachim et al. <sup>12</sup>	1938	31	F	3 mo	Distal half	Present	Not tested	Sudden	Lymph nodes (no autopsy performed)
Seckel <sup>13</sup>	1939	36	M	12 mo	Proximal half	Present	—	Gradual	Generalized
Duff <sup>14</sup>	1939	32	M	3 mo	Whole pancreas	Absent	Not tested	—	Generalized
Duff <sup>14</sup>	1939	60	M	7 mo	Whole pancreas	Absent	Not tested	—	Generalized
Duff <sup>14</sup>	1939	45	M	6 mo	Whole pancreas	Absent	Not tested	—	Generalized
Joslin et al. <sup>15</sup>	1939	58	F	3 yr	Tail	Present	Not tested	Gradual	Liver
Ballinger <sup>16</sup>	1941	53	M	9 mo	Liver	Present	Present	Gradual	Generalized
Finn et al. <sup>17</sup>	1941	45	F	6 mo	Head	Present	Not tested	Gradual	Liver and lymph nodes
Gray <sup>18</sup>	1942	58	F	4½ yr	Tail	Present	Not tested	Gradual	Liver
Quarrier et al. <sup>19</sup>	1942	73	M	21 mo	Tail	Present	Not tested	Sudden	Liver and lymph nodes
Hanno et al. <sup>20</sup>	1943	68	M	19 mo	Tail	Present	Not tested	Gradual	Liver
Holman <sup>21</sup>	1943	45	M	16 yr	Tail	Present	Not tested	Gradual	Liver and lymph nodes
Browning <sup>22</sup>	1943	36	M	14 mo	Body	Present	Not tested	Gradual	Liver and lymph nodes
Brunschwig <sup>24, 25</sup>	1944	32	M	4 yr	Body and tail	Present	Not tested	Gradual	Liver and lymph nodes
Sailer et al. <sup>26</sup>	1946	40	F	3 yr	Body and tail	Absent	Not tested	—	Generalized

received an injection of 1 cc containing the extract of approximately 4 gm of this tissue. The blood sugar values at 0, 30, 75 and 120 minutes after injection were respectively 85, 170, 140 and 85 mg per 100 cc. In the control experiment a rabbit weighing 3 kilograms received an injection of 1 cc containing a similarly prepared extract of approximately 5 gm of normal liver tissue. The blood sugar values at 0, 30, 60 and 120 minutes after injection were, respectively, 75, 75, 70 and 75 mg per 100 cc. No control extract of normal pancreatic tissue was made. It was concluded that no insulin was present in the extracted metastatic tumor tissue.

The salient features of 23 previously reported cases of well established islet-cell carcinoma are presented in Table 1. Cases of reported cancer, without metastases, in which the diagnosis was mainly based on the partial absence of the capsule and pathologic variations suggesting malignancy were not included.

The hospital course in the case reported above was hectic and not conducive to elaborate studies. All efforts were directed toward the prevention of a hypoglycemic death and the preparation of the patient for exploration. Although it was the opinion of the majority of the staff that the hypoglycemia was due to a malignant islet-cell tumor, the suspicious findings in the liver making the outcome of

definite value in the symptomatic treatment of such patients.

In retrospect, certain deductions regarding the cause of the hypoglycemia may be made. Given a case of pancreatic carcinoma demonstrated at autopsy and with three fourths of the liver destroyed by metastases, one is not tempted to invoke other bases for the hypoglycemia. The history of weight loss, asthenia and gastrointestinal symptoms in a patient with sparse axillary and pubic hair, as well as a low concentration of glucose and sodium chloride in the blood, brings up the question of adrenocortical insufficiency, but the autopsy findings did not support such a diagnosis.

Liver dysfunction as the basis of the hypoglycemia merits stronger consideration. Several cases of severe and at times fatal hypoglycemia, for which no explanation was found other than marked histologic liver damage, have been described<sup>7, 28-31</sup>. In the case presented above the liver was seriously involved by metastases, but the ability to excrete bilirubin was unimpaired. Although hepatogenic hypoglycemia is suggested by certain negative considerations, — namely, that insulin was not demon-

strated in the metastases and that beta granules were not demonstrable in the neoplastic cells, — a more plausible explanation is available

The gross and, especially, the histologic characteristics of this pancreatic tumor make its islet-cell origin almost incontestable. The extraordinarily rapid consumption of injected glucose was most impressive. Together, these findings render the diagnosis of carcinoma of the islets of Langerhans with hyperinsulinism difficult to avoid

Extraction of insulin from the metastases would have given the most conclusive proof possible that the tumor was insulin-producing. It is unfortunate that we relied solely on this tissue, much of which may have been necrotic, to the exclusion of the primary site. No conclusion can be drawn from the failure to demonstrate beta granules in the tumor cells. Attempts by various investigators to demonstrate specific granulations in neoplastic islet tissue have in most cases been inconclusive in view of the present meager knowledge of the staining properties of neoplastic tissue<sup>22</sup>

The glucose-tolerance test is usually considered to follow characteristically different forms in hyperinsulinism and hepatogenic hypoglycemia<sup>23</sup>. Fraser, Albright and Smith,<sup>24</sup> however, found the glucose-tolerance test to be unreliable in hyperinsulinism. A study of the test in 11 of the previously reported cases of islet-cell carcinoma with hyperinsulinism failed to show a constant pattern, although a rapid fall to hypoglycemic levels occurred in 8 cases. One cannot make an unequivocal diagnosis of hyperinsulinism on the basis of a glucose-tolerance test, extremely rapid disappearance of the glucose from the blood without appreciable initial hyperglycemia remains, however, strongly suggestive of hyperinsulinism

The use of adrenocortical extract should be briefly noted. The presence of certain features suggestive of Addison's disease and, especially, the need for a more stable supply of glucose made it desirable to supplement the glucose intake with protein and adrenocortical extract. Following these measures the blood sugar rose, but no conclusions can be drawn because of the agonal state at that point.

SUMMARY

A case of severe hypoglycemia, shown at autopsy to have carcinoma of the islets of Langerhans with metastases to the liver, is presented. The possible bases for the hypoglycemia are considered, and it is concluded that the patient suffered from hyperinsulinism

The principal features of 23 previously reported cases of carcinoma of the islets of Langerhans are discussed

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## MEDICAL PROGRESS

### ENDOSCOPY\*

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LITERATURE directly or indirectly related to endoscopy continues to accumulate with amazing rapidity. Each year seems to bring forth additional indications for endoscopic procedures and a wider recognition of their usefulness to the medical profession.

#### ANESTHESIA

According to Clerf<sup>1</sup> the endoscopist employs all types of anesthesia and all methods of induction. It is not always easy to make an endoscopic examination of the air and food passages under local anesthesia, and the casual endoscopist frequently chooses general anesthesia. Routine methods following fixed rules do not make for good anesthesia. As a preanesthetic agent, morphine is valuable whether the anesthesia is to be of local or general type. The barbiturates are also widely used as preanesthetic agents. It is often hazardous to employ local anesthesia in endoscopic procedures in children.

#### BRONCHOSCOPY

*Anatomy* Brock<sup>2</sup> has written an excellent book on the anatomy of the bronchial tree, with special reference to the surgery of lung abscess. This book considers bronchial embolism and posture in relation to lung abscess, as well as the level of the interlobar fissures of the lungs, and then describes the anatomy of each lobe individually. It is well illustrated with photographs, diagrams and roentgenograms. In addition, there are illustrations of bronchoscopic views, as well as diagrams illustrating surface markings and map diagrams of the bronchopulmonary segments.

*Atelectasis* An unusual cause of atelectasis — namely, epistaxis with aspiration of blood — has been reported by Kartagener<sup>3</sup>. This is believed to be the first case of the kind described in the literature.

*Bronchiectasis* Jones, Peck and Willis<sup>4</sup> state that tuberculosis in children is frequently complicated by tracheobronchial tuberculosis. Such bronchial lesions are frequently associated with obstructive pneumonitis. Bronchiectasis, as shown by a bronchogram, was present in 24 out of 34 children, or 70 per cent. The authors consider pulmonary tuberculosis in children to be a common cause of bronchiectasis. Symptoms of bronchiectasis, however, were not

marked, and pneumonectomy was advised in only 1 case.

Olsen<sup>5</sup> believes that bronchoscopy should be performed at least once in every case of bronchiectasis. Bronchial obstructions, such as those resulting from foreign bodies, tumors, broncholiths and broncho-stenosis, may be discovered. The relief of any bronchial obstruction will be helpful. In some cases repeated bronchoscopic aspirations may be beneficial.

*Foreign body* Richardson<sup>6</sup> calls attention to certain pitfalls in the diagnosis and removal of foreign bodies in the respiratory tract. One of the sins of omission is that the physician not only forgets to ask about the possibility of a foreign body but also fails to believe the patient's own story. Fluoroscopy or inspiration and expiration films, or both, are important, especially when a nonradiopaque foreign body is suspected. Unless a foreign body can be completely visualized, it is dangerous to attempt its extraction.

*Adenoma* In a report of 7 cases of bronchial adenoma, Nager<sup>7</sup> states that only 2 patients were over forty years of age at the time of the onset of symptoms. The beginning of the tumor may be associated with the end of puberty. Asthmatoïd wheezing and hemoptysis are often the first signs, with bronchial stenosis, atelectasis and pulmonary suppuration following. Bronchoscopy is essential for early diagnosis. Surgical methods of treatment are indicated for tumor within the deeper layers. Hemorrhage associated with sudden cessation of respiration and death resulted in 2 cases from electrocoagulation.

Von Albertini<sup>8</sup> has studied 10 cases of bronchial adenoma from a pathological standpoint. He believes that there is a close relation between bronchial adenoma and bronchial carcinoma because histologically both seemed to be derived from bronchial epithelium.

Moersch<sup>9</sup> states that adenoma occurs approximately one tenth as frequently as carcinoma of the bronchus. It tends to occur in younger patients than carcinoma does. The average age of patients with bronchial adenoma was thirty-seven years as compared to an average age of fifty-four years in those with bronchogenic carcinoma. Adenoma occurs more frequently in the female than in the male, whereas the reverse is true of bronchogenic carcinoma. The average duration of symptoms before diagnosis of adenoma of the bronchus was

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twenty-six months in his series, whereas the average duration before the diagnosis of carcinoma was eight months. Furthermore, the average life expectancy of patients with bronchogenic carcinoma was, in his experience, only fifteen months after onset of symptoms, and that in cases of adenoma is much longer. Probably the most valuable single aid in the differential diagnosis of bronchial adenoma is bronchoscopy in the course of which tissue can be obtained for positive microscopical diagnosis.

Tinney<sup>10</sup> has found that opinions differ concerning the most satisfactory method of treating bronchial adenoma. In general, the decision rests between endoscopic removal and extirpation of the lesion by means of lobectomy or pneumonectomy. Conservative treatment is recommended if the adenoma is attached to the bronchial wall by a narrow pedicle, is movable and is situated in a bronchus that can be adequately and thoroughly visualized bronchoscopically. When the adenoma is situated so close to the carina that the usual operative measures are impossible, removal of the tumor with the bronchoscope is indicated. Bronchoscopic treatment is indicated when the general condition of the patient is such that lobectomy or pneumonectomy is unduly hazardous. Patients who have been treated by this method should undergo bronchoscopic examination at least once a year so that any recurrence of the adenoma may be found early. If the tumor that has been treated bronchoscopically tends to recur, it is not advisable to continue the bronchoscopic treatment. The advantage of removal of the tumor by means of lobectomy or pneumonectomy is that after the lesion has been removed by this method recurrences are rare, whereas recurrences are comparatively frequent after removal through a bronchoscope.

McDonald,<sup>11</sup> in a discussion of the pathologic aspects of adenoma, believes that there is a tendency for adenoma of the bronchus to infiltrate the bronchial wall and the peribronchial tissues. In 13 of the 15 cases in which the lung was available for study, such invasion had occurred. In the remaining 2 cases there was no infiltration of the neoplasm into the bronchial wall peripheral to the bronchial cartilage, the main mass of tumor being within the lumen of the bronchus. Adenomas invariably arise from main-stem or large bronchi. The condition of the lung distal to the neoplasm depends on the degree of bronchial obstruction that the tumor produces. No metastatic growths were found outside the thorax in 2 cases of adenoma of the bronchus in which necropsy was performed. In only 1 of the 38 cases was a local hilar lymph node involved, and that node was adjacent to the neoplasm.

Clagett<sup>12</sup> believes that the most satisfactory treatment of adenomas can be achieved by the co-operative efforts of the bronchoscopist and the thoracic surgeon. Bronchoscopy must always be

performed at least once and often several times to obtain specimens for accurate pathological diagnosis and to remove at least enough of the growth to relieve the obstruction of the bronchus so that the atelectatic lung can become aerated and any infection distal to the tumor can be drained effectively. In cases in which all or nearly all the visible tumor can be removed bronchoscopically and in which there is no serious damage to the lung distal to the growth, particularly if the patient's general physical condition contraindicates thoracotomy and pulmonary resection, there is no serious objection to this method of treatment. The patient who is treated by bronchoscopic removal of the tumor must be prepared to accept repeated bronchoscopic examination, however, since the tumor sometimes recurs and removal may be required every few months or years. The bronchoscopic treatment is not without risks and difficulties. These tumors are vascular, and serious hemorrhage is occasionally encountered. Since the risk of pulmonary resection has been reduced so greatly in recent years, Clagett believes that the great majority of bronchial adenomas are best treated by pulmonary resection. These are growing tumors, whether or not they are malignant. Often, the portion of tumor outside the bronchus is larger than the intraluminal portion so that only a small part of the tumor can be removed bronchoscopically. In many cases, by the time the tumors cause symptoms that cause the patient to seek diagnosis, the lung distal to the adenoma has already been seriously damaged. The lung is atelectatic and infected, extensive bronchiectasis or fibrosis is frequently present. Pulmonary abscess, empyema and brain abscess are not rare complications. Resection has the advantage that it can be carried out in one stage, and further examinations and treatment are not necessary. Unless the situation of the adenoma makes pneumonectomy necessary, lobectomy is adequate, since the slow-growing, benign nature of these growths makes extensive resection of the lung unnecessary. The age group in which adenomas are found makes the patients particularly good candidates for resection since they tolerate the operation well. With the modern technic for pulmonary resection the operation can be carried out with a risk of only about 5 per cent.

*Lipoma.* Watts, Clagett and McDonald<sup>13</sup> have discussed bronchial neoplasms that, although histologically benign, may, through occlusion of a bronchus, give rise to atelectasis and often fatal suppuration in the tissue of the lung distal to the occlusion. The authors considered particularly a case of lipoma of the bronchus and stated that fat is a normal component of the bronchial wall. Fat is often present in the smaller bronchi until they reach the diameter of 1 mm. Fat may also be found in adenomas. In fact, fat occurs in association with other tumors far more frequently than it occurs alone. In the case reported a diagnosis of pulmonary

tuberculosis was made from the roentgenograms of the thorax, but tubercle bacilli were not found in the sputum. At bronchoscopic examination, a thick purulent secretion was observed in both main bronchi but no obstructing lesion could be seen. Because the lesion seemed to be confined to the upper lobe of the left lung, it was decided to perform exploratory thoracotomy. The upper lobe was atelectatic and was removed. Examination of the removed lobe by the surgical pathologist revealed a soft, gray, pedunculated tumor, 2 cm in diameter, in the main bronchus of the upper lobe of the lung, it was attached to the wall by a narrow pedicle, completely occluding the lumen. Microscopically, the entire tumor consisted of lobules of mature fat cells supported by a delicate fibrous stroma.

**Carcinoma** Guerra, Rousseau, Daumy, Amat and Aguirre Medrano<sup>14</sup> report 4 cases of carcinoma of the trachea. They believe that there is a low incidence in the trachea, especially as compared to carcinoma of the larynx. About half the tracheal tumors occur in the lower third.

In a study of primary lung tumors Adams<sup>15</sup> reported that 54 per cent of the group were epidermoid carcinomas, 13 per cent were adenocarcinomas, 4 per cent were oat-cell carcinomas, and 11 per cent were undifferentiated, 18 per cent could not be classified. Bronchoscopy was positive in 72 of 84 cases of epidermoid carcinoma (86 per cent), negative in 3 cases and not done in 9. Clinically, epidermoid carcinoma of the lung tends to have a slower course than other types of carcinoma. The propensity of adenocarcinomas toward cerebral metastasis is striking. The outlook for arrest of disease by resection is best in the epidermoid group, becoming progressively unfavorable throughout the other groups.

According to Wandall,<sup>16</sup> the demonstration of tumor cells in the sputum allows definite establishment of the diagnosis of carcinoma in about four fifths of cases of primary pulmonary cancer. The specimen must be from the bronchi and must not be allowed to stand for more than eight hours. By the use of bronchoscopic biopsy and by examination of the sputum, the diagnosis of carcinoma of the lung can be verified in about 90 per cent of cases. Sometimes, exploratory thoracotomy may be necessary.

Herbut and Clerf<sup>17</sup> have also made a cytologic study of bronchoscopically removed secretions in bronchogenic carcinoma. In 30 consecutive cases bronchial secretions were stained by the Papanicolaou technic. Cancer cells were demonstrated in 22 cases, or 73 per cent. In the same series a positive morphologic diagnosis from a study of tissue removed endoscopically was obtained in 11 cases, or 36 per cent. Cancer cells were present in the secretions in 7 cases in which bronchoscopy was negative. Sputums were examined in 5 cases in

which cancer cells were present in bronchial secretions, and in only 1 of these were neoplastic cells found. The authors, therefore, consider examination of bronchial secretions for tumor cells superior to examination of sputum. The method is presented not as a substitute for but as an adjunct to the means already employed in the diagnosis of pulmonary carcinoma. It is particularly useful in cases in which the tumor is located at the periphery of the lung or in the upper lobe.

**Sarcoma** Cote<sup>18</sup> reports the case of a sixty-six-year-old woman with pulmonary sarcoma in whom the diagnosis was made only after three bronchoscopies. The left lung was collapsed, and after the first bronchoscopy it became aerated with improvement in the patient's condition, microscopical study of the biopsy, however, did not give a positive diagnosis. A month later the symptoms recurred and bronchoscopy was performed a second time, but again the pathologist could not make a positive diagnosis. Six weeks later, bronchoscopic biopsy showed fibrosarcoma. The patient died within six months of the first bronchoscopy, and autopsy revealed a fibrosarcoma completely occluding the left main bronchus and partially occluding the right main bronchus. No metastases were demonstrated.

**Tuberculosis** Janes<sup>19</sup> has written editorially regarding lobectomy and pneumonectomy in the treatment of pulmonary tuberculosis, stating that patients with well marked bronchial stenosis should be submitted to lobectomy or pneumonectomy provided the disease in the remainder of the lung is sufficiently healed or quiescent. The operation should not be undertaken if it will necessitate the division of the bronchus through a site of active disease.

Sweet<sup>20</sup> reported 27 cases of lobectomy and 36 cases of pneumonectomy in pulmonary tuberculosis. Bronchoscopy was used freely as a diagnostic measure whenever bronchial disease was anticipated. In general, the best results in this series followed pneumonectomy in cases of bronchostenosis and thoracoplasty failure, and lobectomy in those patients who might otherwise have been treated by thoracoplasty.

Overholt et al<sup>21</sup> also discussed pulmonary resection in the treatment of pulmonary tuberculosis. They mentioned the importance of the presence or absence of endobronchial tuberculosis in deciding the type of operation to be performed. They believe that bronchoscopy should be performed routinely following resection to ascertain the condition of the bronchial stump.

**Broncholithiasis** Barrett<sup>22</sup> states that the term broncholithiasis is defined as the formation of calculi in a bronchus and that it has become diagnostic for any patient with a bronchial calculus. It has been stated that tuberculosis is the disease in which broncholiths are likeliest to arise. The symptoms are those of bronchial obstruction. In

all cases in which broncholith is suspected, a bronchoscopic examination should be made.

Clerf, Fox and Fields,<sup>1</sup> have reported 10 cases of broncholithiasis originating from calcified caseous tuberculous areas in the pulmonary parenchyma or lymph nodes, from inspissated pus of a lung abscess or an empyema and from calcified cartilages of the trachea and main bronchus. All patients were bronchoscoped, 8 patients expectorated a broncholith spontaneously, and in 5, one or more broncholiths were removed by bronchoscopy. Residual cylindrical bronchiectasis was the most frequent complication.

Zahn<sup>23</sup> has also reported a case of broncholithiasis. He believes that considering the frequency of calcification in tuberculosis, it is rather surprising to note the low reported incidence of broncholithiasis. In over 4000 cases of pulmonary tuberculosis the case reported was the only example of broncholithiasis.

**Allergy.** Leil<sup>24</sup> regards bronchoscopy as an aid in the diagnosis and treatment of allergic pulmonary disease. It is essential to rule out the possibility of foreign body before the diagnosis of bronchial asthma is made. In a series of 176 children observed bronchoscopically because they presented symptoms of asthma, 18 had foreign bodies in the respiratory tract, 5 had such objects in the esophagus, and 23 had other organic changes. The majority of the patients in status asthmaticus who were observed bronchoscopically showed a marked hemorrhagic and edematous appearance of the mucous membrane of the trachea and both main bronchi, with the presence of thick, tenacious secretion. In addition, most of the patients showed collapse of the posterior tracheo-bronchial wall. Bronchoscopic aspiration of the pulmonary secretion of patients in status asthmaticus who do not respond to medical treatment may often be a lifesaving measure. Oxygen administered through the bronchoscope during the aspiration relieves the dyspnea. One hundred and two patients with status asthmaticus were treated from one to twelve times each, or a total of 259 bronchoscopies with 1 death half an hour after bronchoscopy. The patient who died had previously undergone bronchoscopic treatment twice, with definite relief of symptoms. For six weeks during which the patient was in constant acute asthmatic attacks, bronchoscopy was deferred by a different attending physician. At that time the patient was unable to cough up any secretion, and as a last resort bronchoscopy was undertaken. The bronchoscopic examination revealed that the trachea and both the right and left main bronchi were completely filled with gelatinous, sticky secretions, of which at least 125 cc was aspirated. Immediately after the bronchoscopic procedure the patient seemed considerably relieved. He was being returned to the ward when he suddenly collapsed and stopped breathing. Post-mortem examination revealed advanced pulmonary

and generalized systemic changes. Despite the fact that the secretions had just been aspirated, all the smaller bronchi and bronchioles were occluded by organized plugs of mucus that could be stretched like a rubber band. To have helped this patient, the bronchoscopic aspiration should have been carried out when it was first recommended, and not four weeks later.

## ESOPHAGOSCOPY

### *Congenital Anomalies*

Vinson,<sup>25</sup> in a report on the incidence of esophageal disease in Negroes, calls attention to the fact that lesions in the esophagus that may have originated in congenital abnormalities were encountered more frequently in the White than in the Negro patients, whereas other lesions occurred with equal frequency, in accordance with the density of population. He suggests that congenital deformity may be rarer in Negroes because of the universal presence of the Rh factor in that race.

Gross and Scott<sup>26</sup> reported the case of a two-day-old male infant treated surgically by closure of the tracheoesophageal fistula and oblique anastomosis of the esophageal segments. The child did extremely well for a year and then had some difficulty in swallowing solid food. Esophageal dilatation was necessary. The child was in excellent health at twenty months of age.

### *Esophagitis*

In a contribution to the roentgenologic diagnosis of limited esophagitis, Welin<sup>27</sup> states that the dominant symptom is progressive dysphagia. Substernal pain and eructation of phlegm were also noted in some of the patients. Esophagoscopy findings were divided into three different stages. In the initial stage the inflammatory process is less violent, and the changes are limited to an edematous, slightly bulging and easily bleeding mucous membrane. In the second stage the mucosa of the more or less narrowed lumen is inflamed and fibrin covered. In the final or healing stage, the mucosa is thin, pale and scarred, the wall being sclerotic and shriveled. The increasing infiltration produces progressive contraction of the lumen, which in the final stage may become completely obliterated. Esophagoscopy with biopsy is recommended. Welin presents numerous x-ray reproductions of the various stages and states that in these cases the question for roentgenologists is to find signs differentiating the condition from cancer. It should be pointed out, however, that no matter how smooth and benign the process may appear on x-ray study, esophagoscopy is definitely indicated in every case to rule out carcinoma by biopsy and also to carry out bougienage, which is usually a satisfactory form of treatment.



### Benign Stricture

Benedict<sup>28</sup> has reviewed the cases of 44 patients with benign stricture of the esophagus. The fact that almost all patients were fifty years old made it exceedingly important to rule out carcinoma by esophagoscopy and biopsy. The disease is relatively infrequent in women. In this series there were 31 men and only 13 women. The benign stricture was associated with a hiatus hernia in 17 cases, with duodenal ulcer in 15 and with esophageal ulcer in 8. Treatment included bouginage through the esophagoscope, local application of sulfadiazine at the time of esophagoscopy, dietary management using only bland, strained foods with complete elimination of alcohol and tobacco and, later, the use of a bougie passed over a previously swallowed thread as a guide. It cannot be too often emphasized that blind bouginage is extremely dangerous. The results of proper treatment are usually satisfactory but depend on the severity of the inflammation and on the degree of co-operation from the patient.

In a recent case the treatment of benign stricture of the esophagus by esophagoscopy and bouginage was stated to be generally satisfactory.<sup>29</sup> The patient, however, had been operated on surgically, and the stricture resected without the benefit of esophagoscopy and bouginage. In this connection, Sweet<sup>29</sup> emphasized the danger of possibly missing a cancer of the esophagus by conservative treatment and also brought out the fact that there had been a recurrence of esophagitis in 1 or 2 cases following resection of a benign stricture.

### Cardiospasm

Savinykh<sup>30</sup> considers esophagogastric anastomosis an important procedure in the treatment of cardiospasm, and states that more than a third of the patients with cardiospasm require operative procedures. I do not agree, believing that most cases are well handled by bouginage with the Hurst mercury bougie. Savinykh does not give adequate data regarding medical management and bouginage. It appears that some patients were operated on prematurely.

Grimson et al.<sup>31</sup> reported 9 cases of achalasia treated by esophagogastric anastomosis or cardioplasty. Medical treatment had been used in most cases prior to operation, but it is not clear from the case reports that medical treatment with bouginage had been adequately carried out. Cardioplasty seems to have given fairly good results, but the follow-up period in some cases was rather short. I believe that most cases of achalasia or so-called "cardiospasm" can be treated fairly satisfactorily by a combination of general medical care, esophageal lavage, esophagoscopy if necessary, bouginage with the mercury bougie and sometimes judicious use of psychiatry.

### Peptic Ulcer

Allison<sup>32</sup> believes that peptic ulcer of the esophagus occurs when there is such a derangement of the mechanism of the cardia of the stomach that acid gastric juice flows back easily. The disorder that predisposes to ulceration is hernia of the stomach through the diaphragmatic hiatus into the posterior mediastinum. When the lower esophagus is being constantly bathed by acid from the stomach, a well defined series of changes is found. The first is a recurrent acute esophagitis, which passes on to a chronic esophagitis with recurrent acute ulceration. In the next stage an acute ulcer progresses to a typical chronic ulcer. The ulcer, with its surrounding induration, causes stenosis, and above this stricture there is intense superficial inflammation. Finally, a dense fibrous stenosis is produced. The treatment of a peptic ulcer of the esophagus is by the general medical measures used for ulcer of the stomach. When stenosis is present, repeated esophagoscopy and dilatations may be necessary. When blockage of the narrowed lumen is due to such foreign bodies as raisins, peas or fruit stones impacted in the stricture, relief is more marked, or there may be narrowing due to fibrous stricture from partial healing of the ulcer, in such cases dilatations often give a more prolonged result. The blind passage of bougies is mentioned only to be condemned. Allison states that on theoretical grounds it seems unjustifiable to apply the operation used for carcinoma of the esophagus to stenosis associated with an active ulcer and thus to leave a patient with the deformity that produced, or predisposed him to, the original ulcer. It was decided, therefore, that excision of the affected part of the esophagus was justifiable only if a means could be found for lengthening the esophagus and reducing the stomach below the diaphragm. A loop of small intestine isolated on its mesentery according to the method of Roux recently used extensively by Yudin, seemed to be the most practicable. The operation was first tried on a patient with carcinoma of the fundus of the stomach causing esophageal obstruction. Allison's conclusions are as follows:

Where the lower end of the organ is frequently subjected to digestion by acid gastric juice, peptic ulcer of the esophagus occurs. This happens where inefficiency of the diaphragm allows the stomach and abdominal esophagus to slide up into the mediastinum. Such herniation may be congenital or acquired. Where medical and assisted medical measures fail to relieve symptoms, the length of the esophagus may be restored and the stomach replaced in the abdomen. The size of the hiatus may be diminished to maintain the organs in their normal position. When chronic ulceration and fibrosis lead to inelasticity of the esophagus, reduction of the anatomic deformity may not be possible. The lower end of the esophagus may then be excised and continuity restored by a loop of small intestine on an elongated mesentery.

It seems probable that almost all cases of benign stricture of the esophagus, with or without peptic ulcer, can be treated by medical measures in addi-

tion to esophagoscopy and bouginage, and the indications for surgery in benign ulcers or strictures of the esophagus are therefore believed to be few

Diaz and Riera<sup>22</sup> reported 7 cases of esophageal peptic ulcer in 1 of which there was associated esophageal cancer. The roentgenologic and endoscopic findings were analyzed

### *Lye Stricture*

Hanckel<sup>23</sup> treated 4 cases of recent lye burns of the esophagus by the Salzer technic, and all patients recovered without stricture formation. The Salzer method advocates the early use of soft-rubber bougies in graduated sizes, filled with either mercury or lead shot, to prevent the formation of esophageal strictures. The details of the procedure are discussed. Esophagoscopy should be done in all cases but, to avoid perforation, should be avoided for several weeks after the burn. Barium studies under the fluoroscope are also indicated at frequent intervals

Sweet<sup>24</sup> reported subtotal esophagectomy with high intrathoracic esophagogastric anastomosis in the treatment of extensive cicatricial obliteration of the esophagus. Three patients who had suffered cicatricial obliteration of a large portion of the esophagus as a result of chemical burns were treated by radical esophagectomy. In cases of intractable stricture of the esophagus resulting from chemical burns an esophagectomy followed by a high intrathoracic esophagogastric anastomosis is superior anatomically, physiologically and psychologically to any form of external esophagoplasty as a method of restoring the functional continuity of the upper alimentary canal

### *Foreign Body*

Bernstein<sup>25</sup> reported the removal of a *tortilla* from the esophagus — a *tortilla* is a thin, flat, unleavened cake, such as one of maize, baked on a heated iron or stone. At a point just below the cricopharyngeal muscle esophagoscopy revealed a translucent, doughy, grayish mass to be completely occluding the esophageal lumen. Because of the composition of the mass, it was believed that the usual biting and grasping forceps would be of no avail. The esophagoscope was passed farther, and the mass circumscribed in its lumen, where it became firmly attached to the metallic walls and was withdrawn with the esophagoscope. The mass was 15 by 8 mm.

Holmes<sup>26</sup> presents the case of a ten-year-old boy who ate a piece of apple pie containing a fine steel wire that caused moderate pain on swallowing. X-ray study showed the wire to be to the left of the midline and at the level of the junction of the fourth and fifth cervical vertebrae lying transversely. The patient was given penicillin. Examination of the pharynx and esophagus under ether anesthesia was negative. Further x-ray films about

two weeks after the accident showed the foreign body to have migrated anteriorly, where it could be felt to the left of the thyroid cartilage. Under local anesthesia, it was extracted through a small incision.

### *Perforation*

Gre<sup>27</sup> reported 2 cases of mediastinitis caused by perforation of the esophagus, with recovery after treatment with penicillin. In the first case the perforation followed instrumental dilatation of the esophagus for a stenosis after nitric acid ingestion, and in the other perforation occurred at the cricopharyngeal level after esophagoscopy. The importance of blood transfusion, intravenous therapy and penicillin therapy was emphasized. Before the advent of chemotherapy, mediastinitis was almost uniformly fatal but is now usually curable without surgery.

### *Spontaneous Rupture*

Elason and Welty<sup>28</sup> observed spontaneous rupture of a presumably normal esophagus in 3 cases during a one-year period. They regard the condition as more frequent than is usually appreciated. It is due to sudden increase in pressure. Rupture usually takes place during an episode of vomiting often precipitated by a bout of drinking or a heavy meal. The patient experiences sudden severe pain high in the upper abdomen or epigastrium or beneath the sternum. There may be a sensation of something tearing or giving way in the chest. On examination the patient is found to be obviously critically ill and in profound shock with extreme thirst. In the cases reported all the patients died. The authors believe, however, that with early diagnosis by roentgenography and esophagoscopy in questionable cases and by improved technics in anesthesia, transfusions and chemotherapy, recoveries will soon be reported.

### *Scleroderma*

Rafsky and Herzig<sup>29</sup> have reported 2 cases of scleroderma with esophageal symptoms and cardiospasm. In one of these cases an esophagoscopy biopsy confirmed the diagnosis. Dysphagia was a prominent symptom in a seventy-three-year-old woman but was intermittent in a thirty-two-year-old man. In the first case x-ray examination showed the lower half of the esophagus to be markedly dilated, with spasm at the cardia of the stomach. In the second patient the radiologist demonstrated spasm of the lower third of the esophagus, with temporary obstruction at the cardia. Specific treatment was not discussed.

Olsen, O'Leary and Kirklin<sup>30</sup> state that approximately 10 per cent of patients suffering from scleroderma have complaints referable to the esophagus — usually dysphagia — and sternal burning after meals. The

sclerosis of the connective tissue of the esophagus. Disturbances of the autonomic nervous system may play some part in the causation. The treatment consists of the passage of sounds over a previously swallowed thread as a guide.

### Feeding-Tube Stenosis

Holinger and Loeb<sup>42</sup> observe that severe laryngeal obstruction occasionally results from the routine use of nasal feeding or gastric-suction tubes. Fortunately, this complication is rare, it is so severe when it does occur, however, that it is essential to be aware of the possibility of this complication and to recognize its beginning symptoms at once. Four cases are presented. In 3, rubber nasal stomach tubes were used for four, seventeen and seven days, respectively, during which the patients complained of discomfort due to the tube. Symptoms increased with sore throat, pain radiating into the ears, pain on swallowing, hoarseness and finally dyspnea. Tracheotomies had to be done in these cases four to six weeks after removal of the stomach tubes. All the patients developed severe chronic laryngeal stenoses. One has been extubated, one wears a valve tracheotomy tube, and the third is still under treatment. The fourth patient died as the result of extensive carcinomatosis and mediastinitis. Post-mortem examination demonstrated the ulcer, which had not as yet caused laryngeal destruction.

A review of the literature reveals 24 recorded cases similar to those described above. Treatment consists of removing or changing the position of a feeding tube if the patient complains of a sore throat, especially if hoarseness or pain in the ears develops. Active treatment, aside from chemotherapy, consists of tracheotomy, drainage and subsequent laryngeal dilatation or plastic repair.

### Tuberculosis

In spite of the fact that the esophagus may be continuously bathed by saliva containing tubercle bacilli, tuberculosis of the esophagus is rare. Hamburger<sup>43</sup> states that up to 1926 only 116 cases had been reported. Tuberculosis of the esophagus may develop as a result of the swallowing of infected saliva by direct propagation of tuberculosis of the larynx, by penetration of a tuberculous lymph node through the wall of the esophagus and by the blood stream or lymphatic vessels. The disease may be ulcerative or sclerotic, with or without stenosis. The upper third of the esophagus is involved most frequently, and the lower third least frequently. The best diagnostic results are obtained by endoscopy.

### Varices

Tolan<sup>44</sup> reported several cases of esophageal varices treated by the injection of sclerosing solutions. He believes that the procedure has definite merit, but sufficient time has not elapsed to determine with accuracy its efficacy.

### Carcinoma

Jacobsson<sup>45</sup> presents the case of a patient with carcinoma of the esophagus who was alive and free from evidence of tumor six years after x-ray treatment. He was fifty-eight years old when first seen in 1939. Biopsy showed squamous-cell carcinoma with low differentiation. More than six years after the treatment the patient was cured locally, had no difficulty in swallowing and had no noticeable metastases.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 33291

#### PRESENTATION OF CASE

**First admission.** A fifty-seven-year-old woman, an office worker, entered the hospital because of jaundice.

She had been in good health until two months before admission, when she had caught a cold and had had coryza and hoarseness lasting a few days. As the episode subsided she noted a persistence of lassitude and easy fatigability. Six weeks before admission anorexia and weakness became so severe that she discontinued work. After a shaking chill with nausea and vomiting a physician found the temperature to be 101°F and prescribed sulfadiazine tablets, of which the patient took eighteen without improvement. Three days later she had an attack of severe colicky pain in the right upper quadrant, without radiation, that lasted half an hour and was accompanied by slight nausea. She described this as the severest pain she had ever experienced. A second physician was consulted and found jaundice and an enlarged, tender liver. Subsequently, the patient noticed dark urine and stools that were somewhat light. The jaundice persisted, and a few weeks later pruritus developed. She had lost approximately 10 pounds during the illness.

The past history revealed no serious illness. The diet had been adequate. There had been no fat intolerance. She denied alcoholism.

Physical examination revealed a well developed and well nourished, slightly dehydrated woman in no acute discomfort. The skin and sclerae were moderately icteric. The heart and lungs were normal. The abdomen was slightly protuberant, with tenderness and voluntary spasm in the right upper quadrant. The liver edge was palpable six

fingerbreadths below the costal margin. The spleen was not felt. There was no fluid or edema.

The temperature was 102°F, the pulse 104, and the respirations 24. The blood pressure was 160 systolic, 85 diastolic.

Examination of the blood revealed a red-cell count of 4,000,000, with a hemoglobin of 14.2 gm, and a white-cell count of 9000, with a normal differential count. The specific gravity of the urine was 1.022, with a ++ test for albumin, a green test for sugar and a ++++ test for bile. The stools were brown, several showing +++ guaiac tests. The total protein was 6.5 gm per 100 cc, with 4.0 gm of albumin and 2.5 gm of globulin, the cholesterol 263 mg, the cholesterol esters 127 mg, and the nonprotein nitrogen 26 mg per 100 cc, the van den Bergh reaction was 9.9 mg per 100 cc direct and 12.7 mg indirect, the amylase 25 units, and the alkaline phosphatase 19.5 Bodansky units per 100 cc. The prothrombin time was 27 seconds (normal, 15 seconds). The cephalin-flocculation test was normal, and the thymol turbidity 1.7 units.

A gastrointestinal series was normal except for a diverticulum in the third portion of the duodenum. The spleen was normal in size. The gall bladder contained five small, irregular calculi and filled with dye of diminished density. No calculi were visualized in the region of the common duct. A film of the chest showed areas of increased density occupying the right lower portion of the chest, consistent with collapse of the lower and the greater portion of the middle lobes, with a small amount of fluid.

During the first two weeks there were intermittent spikes in temperature to 103 and 104°F, with chills and a white-cell count rising as high as 34,000, with 95 per cent neutrophils. On a high-carbohydrate, high-protein and moderately low-fat diet, vitamin K and penicillin therapy, the patient gradually improved. The jaundice slowly disappeared. The temperature returned to normal, and x-ray examination showed improvement but considerable persisting density in the right lower portion of the chest.

An aspiration biopsy of the liver on the tenth hospital day showed bile stasis and mild cholangiolitis.

The clinical improvement was reflected by a return to normal of the prothrombin time and urine urobilinogen and by a disappearance of bile from the urine.

Thorotrast studies revealed no evidence of liver abscess and a normal-sized spleen

The patient was discharged to await improvement of the pulmonary condition

*Second admission* (four weeks later) At home she felt increasingly well, gaining 15 pounds She noted a persistent "catching" pain in the right upper quadrant, however, which seemed to improve after eating There had been no recurrence of jaundice or colic

Physical examination was negative except for a tense abdomen with an increased area of dullness in the right upper quadrant The liver edge was not palpable

On the second hospital day an operation was performed

#### DIFFERENTIAL DIAGNOSIS

DR ROBERT R LINTON May we see the x-ray films?

DR TOUFIC KALIL The biliary stones seen in this first film and on later films, appear to be contained within the gall bladder It was thought that one of them was a little too far from the others to lie within the gall bladder In the first gastrointestinal series, apparently, there was a great deal of food in the stomach, and the collection of barium was thought to be a diverticulum of the third portion of the duodenum A repeat gastrointestinal series with an empty stomach showed no evidence of a lesion — the "diverticulum" had disappeared The first chest films show an area of atelectasis in the right lower lobe, and a film taken later shows considerably more atelectasis and some fluid I do not believe that the middle lobe is definitely collapsed, but there is some collapse in the lower lobe, as well as fluid

DR HELEN S PITTMAN May I make a correction? My recollection is that the signs in the chest appeared after the liver biopsy and not spontaneously Dr Volwiler is in agreement with that statement, I believe

DR WADE VOLWILER Yes

DR LINTON This case presents a problem in biliary disease, and the following points are of interest. There was a short history of chills, fever, nausea and vomiting, dark urine, jaundice and light-colored stools Associated with these symptoms was a severe attack of pain in the right upper quadrant without radiation The patient had lost only 10 pounds in weight, and that had been coincident with the present illness She apparently had not had a chronic disease over a period of years that had caused her to be run down In my opinion a history of chills, fever, nausea and vomiting, jaundice, light, clay-colored stools and pain in the right upper quadrant is pathognomonic of cholelithiasis, choledocholithiasis and cholangitis I am slightly suspicious of these diagnoses, however, in view of the fact that the case is being discussed before this group In confirmation of the history and these diagnoses, however, are the facts that the patient was jaundiced on entry and that there were

tenderness and spasm and a questionable mass in the right upper quadrant, which was taken to be the liver The mass was felt six fingerbreadths below the costal margin It is possible that this was an inflammatory mass involving the gall bladder, but the physical examination seems so definitely to indicate that it was the liver that we must accept the statement The fact that x-ray examination of the gall bladder shows only a small gall bladder is also confirmatory In addition, the gall bladder was visualized by the Graham test — an indication that it was functioning to a certain extent I think that a completely inflamed gall bladder rarely concentrates dye, if the dye ever gets into it.

It is interesting that the spleen was not enlarged, since there have been a number of cases in which that has been demonstrated It could not be felt on physical examination and did not appear enlarged on the plain film, the Thorotrast examination, which should have visualized the spleen, again failed to demonstrate it I speak of that because it seems to me that one can fairly well rule out cirrhosis of the liver as the cause of the symptoms and the jaundice In addition, apparently, the patient did not have ascites, although that does not necessarily rule out cirrhosis, which can occur without ascites

The laboratory studies are of interest in that the hemoglobin and the red-cell and white-cell counts were normal, which indicate that this was not a neoplastic lesion The blood chemical findings, so far as I can tell, were essentially normal, except for the van den Bergh reaction, which was markedly increased, the direct reaction being 9.9 mg per 100 cc and the indirect 12.7 mg, giving a total of 22.6 mg, which in my experience indicates a rather severe jaundice The alkaline phosphatase was elevated — 19.5 units, which is far above normal What its diagnostic significance is, I am not entirely sure I do know that in obstructive jaundice an elevation of the alkaline phosphatase occurs The prothrombin time, which is of especial interest to the surgeon as a liver-function test, was elevated in this case, indicating considerable liver damage and a tendency toward hemorrhage following any surgical procedure

Another laboratory test that I consider significant was the +++ test for bile in the urine The fact that the stools were brown indicated that the patient did not have complete obstruction of the common bile duct The x-ray studies have been demonstrated to us, and we can see the stones in the gall bladder The chest film showed a slight amount of atelectasis before liver biopsy, indicating presumably that there was some process involving the right lower lobe It is possible that it arose from an inflammatory process beneath the diaphragm I think it unlikely that there was a pulmonary infarct I believe that the disease in the chest played no particular part in the clinical picture, therefore, I shall not consider the chest findings further

On the first admission it was of interest that the patient ran an intermittent fever associated with chills, the temperature going as high as 103 and 104°F. Associated with the fever was an elevated white-cell count, up to 34,000, indicating sepsis somewhere. After admission the patient was placed on a conservative regime and improved sufficiently so that it was not thought necessary to do an emergency operation.

The liver biopsy was essentially normal except for cholangitis and bile stasis. The patient finally returned a month after discharge, and an operation was performed.

It is my opinion that the diagnoses that best explain the history, the symptoms and the physical and laboratory findings are cholelithiasis, choledocholithiasis and cholangitis. A patient rarely has a so-called "Charcot type" of fever with such findings unless they are due to common-duct stone and associated infection in the biliary passages. Carcinoma of the common bile duct or pancreas cannot be entirely excluded. In my opinion, carcinoma of the biliary passages or head of the pancreas usually but not always produces complete biliary obstruction, whereas this patient had an intermittent obstructive jaundice, which in my experience is much likelier to be due to a ball-valve type of stone. I also consider the fact that her condition was fairly good on admission to indicate that she had not been suffering from an extensive malignant lesion.

Another condition that should be mentioned is congenital hemolytic jaundice, which usually occurs or becomes obvious much earlier in life. It is most unusual for a woman of fifty-seven years of age to become jaundiced for the first time because of congenital hemolytic jaundice. In addition, she had a normal-sized spleen, which again is most unusual in this condition. Another possibility is duodenal ulcer, which I believe should be ruled out chiefly on the basis of the x-ray findings and also by the fact that the history was not typical of duodenal ulcer. The diverticulum of the duodenum has been eliminated as a cause, and it could have been a cause only if it had contained some form of infiltrative process that involved the common bile duct by continuity. Infectious hepatitis might also be considered, but I do not believe that I have enough evidence to make that diagnosis. I have ruled out cirrhosis of the liver already by the fact that the patient had a normal-sized spleen and no ascites. I shall therefore stick to my original diagnoses: cholelithiasis, choledocholithiasis and septic cholangitis.

DR PITTMAN: We eventually thought as Dr Linton did and requested a surgical consultation, with the same preoperative diagnosis. When this woman came in we seriously considered infectious hepatitis. Later on, we thought a good deal more of alcoholism because of a story that she and her husband had only egg and sherry for breakfast—we tracked that down but came up against a stone

wall. The patient was seen by Dr Harold P. Himsworth, of London, and perhaps Dr Dahl remembers what he said.

DR LEWIS K. DAHL: Dr Himsworth made a diagnosis of infiltrative carcinoma involving the biliary radicles. He said that he had seen patients with carcinoma of the liver who appeared to be as septic as this patient and yet at autopsy had no sepsis. Therefore, he postulated that this woman had an infiltrative carcinoma of the biliary radicles—an intrahepatic infiltration.

DR VOLWILER: Another reason he made that diagnosis was that the liver appeared huge on the first admission.

#### CLINICAL DIAGNOSES

Cholelithiasis  
Choledocholithiasis?

#### DR LINTON'S DIAGNOSES

Cholelithiasis  
Choledocholithiasis  
Cholangitis

#### ANATOMICAL DIAGNOSES

*Chronic cholecystitis*  
*Cholelithiasis*  
*Choledocholithiasis*  
*Adenocarcinoma of ampulla of Vater*

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY: The operative note of Dr Charles G. Mixer, Jr., was as follows:

Under nitrous oxide, oxygen and ether anesthesia the abdomen was prepared and draped in the usual fashion and entered through a subcostal incision. Exploration of the abdomen was entirely negative except for the gall bladder which was densely adherent to the surrounding structures and was freed up with some difficulty. The bladder was slightly enlarged and contained a number of small stones in the ampulla and in the cystic duct and small stones could be palpated in the common duct. The gall bladder was removed from above downward. The cystic duct was large and was transected close to its entrance into the common duct. The common duct was then exposed. It was markedly dilated being approximately 1.5 cm in diameter. It was incised; it had a thick wall and a number of small stones were obtained from it. When an attempt was made to pass a probe through the ampulla of Vater, however, it was found impossible to do so. On mobilization of the duodenum what was taken to be a stone about 7 mm in size could be felt at the area of the ampulla at the site of obstruction. The stone searchers were used and there was a definite grating as if against a stone but the stone could not be grasped or withdrawn. It was therefore considered advisable to open the duodenum and explore the ampulla which was large and puffy being approximately 7 mm across. It was surrounded by firm hard tissue, and in the center of the opening was a definite area of whitish, hard tissue which was biopsied. This was reported on the basis of a frozen section to be adenocarcinoma. It was therefore decided to proceed with a one-stage Whipple procedure.

The patient is still in the hospital, getting along fairly well, although she seems to have developed a trace of sugar in the urine. There had been occasional evidence of sugar before operation. Whether the resection of the pancreas was actually responsible for the diabetes is doubtful. She may have been

on the verge of diabetes before operation, which was enough to make the diabetes manifest. It has apparently been quite easy to control the glycosuria.

DR LINTON I do not know of any cases of diabetes developing after a Whipple operation.

DR ISAAC TAYLOR This patient had sufficient evidence of decreased glucose tolerance before operation to be considered diabetic.

DR DAHL Certainly, in animals, one can resect a much greater portion of the pancreas without producing diabetes.

DR LINTON This has been an extremely interesting and instructive case of obstructive jaundice. The operating surgeon, Dr. Mixer, is to be complimented on recognizing a carcinoma of the ampulla in the presence of common-duct stones. I still believe that the history, physical examination and hospital course are typical of choledocholithiasis and cholangitis and that the carcinoma was an incidental but, naturally, extremely important finding. I think that it is impossible to say whether there was any relation between the gallstones and the carcinoma. Dr. Mallory could perhaps enlighten us in this regard.

DR MALLORY The association between cholelithiasis and carcinoma of the gall bladder is close—in fact, it is rare to find a carcinomatous gall bladder in the absence of stones. I do not know of any figures concerning the association of cancer of the bile ducts and ampulla to the presence of stones in the common duct. Silent stones are, of course, frequent in the gall bladder, whereas they are certainly unusual in the common duct. It is possible that a stone must be present for years to induce the development of cancer.

## CASE 33292

### PRESENTATION OF CASE

A twenty-two-year-old man entered the hospital because of pain in the legs.

The patient had been in good health until three and a half years before entry, when he began to have bouts of bloody diarrhea associated with abdominal cramps, weight loss and weakness, but the symptoms were not severe enough to require hospitalization. A barium enema and gastrointestinal series three years before entry were negative. Despite a low-residue, bland diet, the patient continued to have similar episodes two or three times a year. His weight, which had been 180 pounds five years before entry, had decreased to 157 pounds a month before entry, and he was still having two or three semiformal bowel movements a day, although he had been improving since the last severe episode eleven months before admission. Five weeks before entry he was awakened by a sharp throbbing pain in the left leg, which seemed to center about the knee but sent "knife-like" radiations down to the toes and up to the hip. The pain persisted for about ten hours but was not

severe enough to keep him from walking, although he limped slightly. During the following week he felt well, but the pain returned and was even severer than previously. After two days in bed he was able to walk again, but the leg was weak and he had to limp, the pain gradually subsided over the course of a week. Three weeks before entry there was another severe exacerbation of pain, which persisted, forcing him to remain in bed except for visits to the clinic. Two weeks later he began to have pain in the right hip, subsequently radiating up and down the leg, similar to that on the left side. Aspirin gave only partial relief. On the day before entry he began to have pain in the jaw. At no time did he have swelling, redness, warmth or tenderness in any of the joints. Since the onset of the pain his appetite had been poor, and he had lost another 10 pounds in weight. He had been feverish but had had no real chills.

The patient had worked for six years as a ship-fitter in the Navy Yard. He did welding and used end lead intermittently as a plumber would. He disliked the work and complained of great fatigue. Six months before entry he took a job tinting photographs and continued with this work until the present illness.

Physical examination disclosed a patient who appeared acutely ill and was pale and sweating profusely, he complained of a dull, steady ache in both hips, as well as pain in the lower left teeth and stiffness in both temporomandibular joints. The heart was normal. There were dullness, decreased breath sounds and decreased tactile fremitus over the left portion of the chest. The abdomen was somewhat distended and firm, but not tympanic or tender. The muscles of the left thigh and leg were diminished in volume when compared with the right. Examination of the cranial nerves was negative, except for numbness to pinprick over the lower lip. The arms and legs were weak, the legs more so than the arms, and the quadriceps muscles were weaker than other groups. The patient was unable to raise the left leg off the bed, and the right was raised with some difficulty. There was no muscle tenderness. The knee jerks were absent. The arm jerks, hamstring and ankle jerks were normal, as were the abdominal and plantar reflexes. Sensation was normal except for the lower lip.

The temperature was 101°F, the pulse 120, and the respirations 20. The blood pressure was 150 systolic, 70 diastolic.

Examination of the blood revealed a red-cell count of 4,300,000, with 11 gm of hemoglobin, and a white-cell count of 7800, with 72 per cent neutrophils. The smear showed considerable polychromatophilia and basophilic stippling. Examination of the urine was negative, including a Watson test for uroporphyrin. The stools were soft and brown and gave a positive guaiac test. Repeated blood cultures were negative, as were a blood Hinton test and agglutination tests for typhoid fever and brucellosis.

The total protein was 6.9 gm per 100 cc, with an albumin of 4.03 gm and a globulin of 1.98 gm, the nonprotein nitrogen 22 mg, the phosphorus 3.2 mg and the alkaline phosphatase 4.2 Bodansky units per 100 cc. The cephalin-flocculation test was negative, and the van den Bergh reaction was normal. The prothrombin time was 17 seconds (normal, 15 seconds). Examination of the spinal fluid was negative.

X-ray examination revealed fluid in the left side of the chest and extending over the right lung in lamellar fashion. There was an area of increased density in the cardiophrenic angle on the left, which on lateral view seemed to be against the interlobar septum in the lower lobe. The abdomen was normal. The lumbar spine showed flattening of the lumbar curve. The knees were normal. An electrocardiogram was normal. A bone-marrow smear showed normal erythropoiesis and myelopoiesis. The gastric juice contained no acid.

On the second hospital day examination showed shifting dullness and a definite fluid wave in the abdomen. On the fourth hospital day a thoracentesis in the left posterior axillary line produced 50 cc of turbid yellow fluid, which became blood tinged as the tapping progressed. The specific gravity of the fluid was 1.019. The white-cell count was 100,000, with 5 per cent neutrophils, 25 per cent small lymphocytes and 70 per cent large mononuclear cells. No organisms were found by gram and Ziehl-Neelsen stains. On the seventh hospital day the patient appeared much worse, although he had been receiving 2 gm of streptomycin a day for three days. He complained of pain in the legs, back, abdomen and chest. The temperature was 102°F, and the pulse 160. A friction rub was heard in the left axilla. He was started on 400,000 units of penicillin a day. On the ninth hospital day a peritoneoscopy was performed. Two liters of turbid, rose-colored fluid, with cytologic findings similar to those in the pleural fluid, were removed. Acid-fast smears were negative. The liver was found to be slightly enlarged, with a rounded, everted edge. No tubercles or tumor was seen. On the fifteenth hospital day the temperature reached 106°F, and the white-cell count had climbed to 28,000. The blood smear showed some abnormal primitive stem cells, some late myelocytes and a few nucleated red cells. The patient gradually failed, and died on the seventeenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

Dr JAMES B. TOWNSEND: This patient had a history of abnormal intestinal symptoms for more than three years before he entered the hospital for the terminal illness. May we see the x-ray films?

Dr TOUFIC KALIL: This, apparently, is the area of increased density against the interlobar septum in the lower lobe.

Dr TOWNSEND: Do you think that it is intrapulmonary and not in the pleural cavity?

Dr KALIL: Yes, there is also pleural fluid.

Dr TOWNSEND: Not so much fluid as I anticipated clinically.

Dr KALIL: Not at that time. Apparently the patient became sicker.

This portable film taken at the bedside shows an increase in the amount of pleural effusion on the left and not much of anything else. This is a film of the abdomen taken at that time, showing an increase in the amount of peritoneal fluid.

Dr TOWNSEND: The films of the old barium enema and gastrointestinal series are not here, I imagine.

Dr KALIL: No.

Dr TOWNSEND: Thoracentesis produced 50 cc of fluid. That is a small amount. I wonder whether it was a diagnostic tap to test the fluid or an attempt to get more.

A PHYSICIAN: It was a diagnostic tap.

Dr TOWNSEND: The specific gravity was 1.019, which indicates an exudate. The white-cell count was 100,000. It must have been a turbid fluid. This was a mononuclear and not a polymorphonuclear type of fluid.

Was anything found on culture?

A PHYSICIAN: No.

Dr TOWNSEND: I do not believe that I shall be able to reach an accurate diagnosis in this case. There are several possibilities that are worthy of discussion, however.

To recapitulate, this young man had been ill for three and a half years, starting with abdominal symptoms including recurring attacks of bloody diarrhea, which progressed to more or less continuous diarrhea, at least for the last few months. He was brought to the hospital by the occurrence of neurologic symptoms: pain in the legs, with weakness and apparent atrophy of the legs and with loss of knee jerks but with the other reflexes essentially normal. The neurologic symptoms were referred to various parts of the body, including the jaw and the lower lip. There is no description of any local inflammatory condition, however, in the region of the mouth or jaw to account for these symptoms. On admission he had fever and presumably had been running an elevated temperature for some weeks before that. He had lost over 30 pounds in weight. Although he had no complaints referable to the chest, the striking physical finding on entry was the presence of fluid in the left pleural cavity, which increased during the hospital stay. The character of the fluid is described, and while the patient was in the hospital considerable fluid developed in the abdomen of the same character as that in the chest. The patient then had a high fever and failed in spite of the use of streptomycin and penicillin. All attempts to find an infectious agent were apparently unsuccessful, and the patient died. Shortly before death the blood stream showed something that had not been present previously — namely, a few nucleated red cells and a few primi-



tive stem cells. Possibly, this was merely a terminal event in a patient extremely ill with other disease that had nothing to do with the hematopoietic system, although we must pay attention to these findings. These were found two days before death. A bone-marrow biopsy was performed, presumably shortly after admission and not close to the time of death.

This patient had generalized symptoms referable to the gastrointestinal tract and the nervous system, evidence of a disturbance in two of the serous cavities and, finally, a blood disturbance, which may or may not have been significant. We must consider three general categories of disease into which this case might fall.

Could there have been some type of neoplasm? The history is rather long for neoplasm in a young man, but there is one category of neoplasm, lymphoblastoma, in which a survival of three and a half or four years is possible. I believe that it is possible for some type of lymphomatous disease to cause most of the symptoms. Bloody diarrhea does not occur frequently in lymphomatous disease, but there are lymphomas of the intestines, particularly of the small intestine, that do bleed and can produce diarrhea and pain. Certainly, lymphomatous disease can cause a neurologic type of disturbance similar to what this patient had. If there is infiltration of the vertebrae, particularly with involvement of the spinal roots as they emerge from the vertebrae, severe pain and atrophy and changes of the type described in this case can occur. Lymphoma can involve the serous cavities. I do not know that I have seen it involve both the pleural and the peritoneal cavities, but I see no reason why this should not be possible. In the last two days of life there was evidence of a blood disturbance suggesting a neoplastic disease—namely, the appearance of nucleated red cells and the primitive stem cells. It is possible that this man had a lymphomatous process, call it "aleukemic leukemia" or whatever you will—something that had remained latent for a long time and finally, in the last few days, showed up in the blood. Nucleated red cells rarely occur even in the terminal stages of any severe type of disease except neoplasm involving bone marrow unless profound anemia is present, which was not so in this case. Nucleated red cells occur quite regularly in the course of any type of leukemia.

The second category of disease is some type of chronic infectious process, a form of granuloma, such as tuberculosis, actinomycosis, blastomycosis or one of the other granulomatous processes. We should also consider tularemia. Tularemia rarely runs a course so long as this. There is a variety of tularemia in which there is no presenting local lesion from which the organism has entered, it is believed that it can infect through the gastrointestinal tract. I have never heard of a case that went on with chronic diarrhea but certainly pulmonary and

pleural lesions occur and the findings may be fairly similar to those in the case under discussion, I think that tularemia is a remote possibility, however.

Every effort was made to locate tubercle bacilli in both the pleural and the abdominal fluid, with no success. There is nothing that I can see in the chest film to suggest tuberculosis of either the apical or the miliary type. If this was tuberculosis, it was a general tuberculosis, and I should expect it to be miliary. Moreover, the normal spinal fluid does not indicate the usual terminal meningitis, which is present in generalized miliary tuberculosis. Dr. Mallory is looking at the x-ray film. I wonder if he sees anything there that I do not see. The roentgenologist did not point out anything that looked like miliary tuberculosis. In spite of these negative findings we have all been caught on generalized tuberculosis, whether miliary or not, and I think that it is a possibility that cannot be excluded. The intestinal symptoms are consistent with it, and I think that practically everything in the case is consistent with that possibility, including the blood changes on the last two days of life. I have seen a patient die of generalized tuberculosis who in the last three or four days of life showed a myeloid picture closely resembling lymphatic leukemia and who was considered not to have leukemia—it was believed that the blood changes were due to extensive tuberculosis, even though this did not apparently involve the bone marrow.

I see no evidence on which to base a diagnosis of actinomycosis. An intestinal lesion that had gone on for that length of time from actinomycosis would undoubtedly have produced a fistula. I think that the pleural fluid would probably have been examined, and the examiners should have been able to find the organism. I see nothing on which we can base the diagnosis of blastomycosis or torulosis, particularly the latter, which does involve the meninges but in which the organism can usually be found. There may or may not be many cells in the spinal fluid. Torulosis usually produces meningeal symptoms, which this patient did not have.

The third category of disease in which widespread symptoms occur is the so-called "collagen-vascular group," including such conditions as periarteritis nodosa and lupus erythematosus. These may go on for a long period and may cause widespread symptoms involving the muscles, as in this patient. I do not know whether they cause bloody diarrhea, however, and I cannot on this picture make a diagnosis of periarteritis nodosa, lupus erythematosus disseminatus or scleredema, although these possibilities should be mentioned.

In closing I am not at all sure what the diagnosis is, but I shall put as my first choice, lymphoma, and as my second, generalized tuberculosis.

DR. WYMAN RICHARDSON: This was a complicated case. I saw the patient only twice in consultation,

when Dr F D Adams was on service I am sorry that he is not present. Since the case was so complicated I said that I would simplify it. It is easy to simplify things by looking at the blood smear. I saw the patient shortly after admission and said that there was a great deal of red-cell regeneration and that it was not compatible with the usual types of sepsis, including tuberculosis. I do not know now what the answer is.

There were three things that I thought of: hemolytic anemia, marrow infiltration and blood loss. The blood loss did not seem to me to be sufficient. There was no evidence of hemolytic anemia. Although the question of lead poisoning came up, I could not see how it could account for the pulmonary picture. That left invasion of bone marrow by tumor, and because of the abnormal white cells, I said that I favored marrow disease, perhaps of the Hodgkin's-sarcoma type or some other rapidly progressive disease involving the marrow. I saw the patient a few days before he died. With this extreme outcropping of immature stem cells, which I could not identify, and some nucleated red cells and identifiable myelocytes, I was fairly certain that he had subacute myelogenous leukemia with a hopeless outlook. I did say, however, not being able to identify the primitive stem cells, that the myelocytosis might be due to marrow encroachment and that I should consider some other type of neoplastic cells, such as those of a Hodgkin's sarcoma. So far as the "group diseases"—lupus erythematosus and so forth—are concerned I have seen some queer pictures in them, but since we do not know what we are talking about when we discuss that group, what is the use of saying anything?

DR TRACY B MALLORY I should like to ask the roentgenologist if he can see anything in the superior mediastinum in this film.

DR KALIL There is one other film, taken two weeks previously, that is perfectly normal, so that whatever developed was in that period. Both pulmonary arteries are prominent, particularly the one on the left. The only other shadow that might be difficult to explain is the one overlying the left pulmonary artery and possibly over on the right, but this is a supine portable film and difficult to interpret so far as that particular shadow is concerned.

#### CLINICAL DIAGNOSIS

Malignant lymphoma

#### DR TOWNSEND'S DIAGNOSIS

Malignant lymphoma

#### ANATOMICAL DIAGNOSIS

*Malignant lymphoma, lymphoblastic type, involving small bowel, appendix, gall bladder, liver, mediastinum, retroperitoneal tissues and bone marrow*

#### PATHOLOGICAL DISCUSSION

DR MALLORY We found a 350-gm tumor mass in the region of the thymus, which I should think would have been visible on the x-ray films. There was tumor in innumerable other areas. One of the older tumors—and I think the primary one—was in the jejunum, 15 cm below the ligament of Treitz. It is quite conceivable that it had been present for three years and accounted for the early intestinal symptoms. There were multiple areas of involvement, chiefly of the serosa of the bowel, but the appendix was completely replaced by tumor, as was the gall bladder. The spleen was normal in size, and the liver was considerably enlarged and irregularly infiltrated with tumor, the large mass of tumor being centrally placed in the region of the falciform ligament and invading in both lateral directions from that point. The retroperitoneal tissues were widely invaded, involving the cortex of one adrenal gland and part of the pancreas, and there were multiple nodules in the kidneys. The bone marrow, which had shown only hyperplasia on biopsy a few weeks before death, showed marked infiltration with tumor cells. The spleen showed hematopoiesis but I cannot convince myself that it contained tumor cells. There were many nucleated red cells and myelocytes, which would adequately explain the blood picture. Histologically, we classified this as a lymphoblastic type of lymphoma. I think that the terminal involvement of the bone marrow was too irregular and hardly diffuse enough to warrant calling it leukemia. We did not explain the neurologic symptoms adequately. The spinal cord was normal, and unfortunately we did not have the peripheral nerves to study.

DR CHARLES S KUBIK Considering the retroperitoneal involvement, I suppose that these pronounced neurologic symptoms, which had segmental distribution, are explained by tumor involvement of the spinal nerves in the region of the intervertebral foramen. This could have been missed at the time of post-mortem examination.

DR RICHARDSON I should like to say that the terminal picture was not that of bone-marrow encroachment. The primitive stem cells in the peripheral blood were undoubtedly tumor cells.

DR MALLORY Yes, I do not doubt that. Everything suggests that the tumor smoldered over a long period at a relatively low rate of growth and that there was rapid and widespread dissemination in the last few weeks of life, especially in the last few days.

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## MEDICAL GROUP PRACTICE

SPORADIC discussions of group practice, according to a paper published elsewhere in this issue of the *Journal*, have been plentiful since the report of the Committee on the Costs of Medical Care was issued in 1932. There has been, however, little critical analysis of factual data. Like the New England weather, group practice has evoked considerable comment with but little constructive action. Increasing interest, nevertheless, is being shown. This type of practice has been stimulated by both wars to the extent that 52 per cent of medical officers, according to a questionnaire of the American Medical Association in 1944, indicated their desire to engage in it after their return from service.

An attempt to define group practice shows that current conceptions of it range from a loose associa-

tion of physicians without organized financial arrangements to medical combinations, owned by one or more of the participating physicians, in which all income is pooled and divided. It is now generally accepted that common use of the facilities for practice, with the inclusion of two or more specialties, and the pooling and redistribution of incomes are necessary to fulfill the requirements.

Types of group practice are variously classified. Thus, one classification is based on ownership or sponsorship, as into private, industrial or hospital groups, and another according to the scope and type of medical service offered, whether into service groups in the strict sense, giving general care to patients, into reference groups furnishing only specialized care to referred patients or into diagnostic groups providing little or no treatment.

The chief argument in favor of group practice is the increasing complexity of modern medical practice. Listed against it are the fact that the general practitioner can still care for 85 per cent of all patients, the more or less cumbersome and often costly mechanism of such associations and the frequent impairment of the personal relation between physician and patient.

Let us hope that the study initiated last year by the United States Public Health Service, of which this paper is an introductory report, may go far toward giving the information we need. As the author writes, the answers must rest on "a foundation of factual data that is now lacking."

Various horse-and-buggy doctors have delivered a number of valedictory addresses in recent years. This does not mean, however, that their method of practice is entirely on the way out. We still have need of their modern prototypes among the various other forms of medical practice that a changing order will require.

## A PASSING ERA IN MEDICAL HISTORY

Six amateur medical historians and book collectors greatly influenced the development of studies in the history of medicine in this country in the first three decades of the twentieth century. With the death of Edward Clark Streeter on June 17, at his home in Stonington, Connecticut, there

passed from the scene the last of the group, originally consisting of William Osler, William H. Welch, Harvey Cushing, Arnold C. Klebs, Casey Wood and Streeter. Only Streeter and Klebs were not actively engaged either in the practice of medicine or surgery or in laboratory research during most of their lives, but both Streeter and Klebs began their medical careers by seeing patients, one in general practice and the other as a specialist in tuberculosis. Osler was primarily a clinician, Welch a pathologist, Cushing a surgeon and Wood an ophthalmologist. In the late years of his life, Osler was actively engaged in the building up of a great library and became a collector of medical books unrivaled in his time. He found time, however, for scholarly studies as illustrated by his papers on Linacre and other medical worthies. Klebs turned more definitely to bibliographic research and the study of incunabula. His lifework culminated in an authoritative handlist of fifteenth-century books on medicine and science. Welch found time to write historical papers of great value, but he had little opportunity to do fundamental research in medical history similar to that done by Klebs and Streeter.

Streeter's work was largely in relation to the Renaissance and the development of medicine during the fifteenth century. He made a profound study of the doctors who practiced in both France and Italy during this period, but his particular interest was in the Florentine physicians. Few men had a wider knowledge of this field of medical history, and with a charming voice and manner, Streeter could talk for hours on a special subject, carrying his listeners along with him with so much enthusiasm that time was forgotten. So intimate was he with our medical forbears that he could bring to the imagination of the listener a vivid picture of Florentine medicine and the doctors who practiced it. Examples of his capacity to interpret the past, unfortunately, were seldom heard in public. It was in the quiet of his home, surrounded by books of his own choosing he knew so well, with a few friends and devoted students, that he was at his best. A section of his library, having to do with pest and fevers, was exhibited in Boston in 1921. The majority of his books ultimately found a fitting home in the library of the New York Academy of Medicine.

The amateur medical historian and book collector, such as these six men exemplified, added a distinct stamp of culture to American medicine. The pre-eminence of Osler and Welch naturally made them leaders in the field. Klebs was less known, since he lived in Switzerland the latter part of his life. He visited this country frequently, however, and being a superb letterwriter, he was in constant communication with his friends in America. Streeter was more of the retiring amateur type than any of the others. When he spoke in public, as he did infrequently, he made a great impression, and his few scholarly papers, particularly the studies on early anatomy with Garrison, will long be remembered.

These men began an era of great achievements in the field of medical history. A movement was instigated that is now widely expanding and changing the aspect of the advancing culture of medical thought throughout the country. Medical-history clubs have sprung up in many areas. Universities are taking recognition of cultural and historical studies in formulating their courses. But with the development of the professional historian of medicine, the era characterized by the amateur of great scholarship, charm, book-collecting instinct and long purse has largely passed with the death of the last of a great band of thoughtful men who made distinct contributions to our medical heritage.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**HOWARD**—Allen R. Howard, M.D. of North Attleboro, died June 4. He was in his sixty-second year.

Dr. Howard received his degree from Cooper Medical College, San Francisco in 1911. He was formerly a major in the Medical Corps, United States Army. He was a fellow of the American Medical Association.

His widow survives.

**KELLY**—William P. Kelly, M.D. of Pittsfield, died April 15. He was in his seventy-seventh year.

Dr. Kelly received his degree from Albany Medical College in 1892. He was a former president of the Berkshire District Medical Society and was a fellow of the American Medical Association.

His widow and two daughters survive.

**O'HARA**—Francis J. O'Hara, M.D. of North Adams, died May 2. He was in his sixty-eighth year.

Dr. O'Hara received his degree from Georgetown University School of Medicine in 1904. He was a former mayor of North Adams and a former member of the board of health. He was medical examiner for the United States Aeronautical Bureau.

A son, a daughter, four grandsons, a brother and a sister survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### SENDING SPECIMENS TO DIAGNOSTIC LABORATORY

Physicians are reminded that the diagnostic outfits distributed when the Bacteriological Laboratory was located in the State House still bear the State House address and therefore will be delayed in reaching their destination unless the address is changed. All outfits on hand should be properly re-addressed to the Bacteriological Laboratory, 281 South Street, Jamaica Plain 30, Massachusetts.

If an early report is urgent, physicians are advised to send specimens by *special delivery* or *messenger*. This is particularly recommended during week ends and holidays, when mails are likely to be delayed.

Reports of new cases of diphtheria — as well as those of other diseases that depend on early bacteriologic diagnosis for proper treatment — are telephoned, without cost to the physician, to any part of the Commonwealth. Unless a telephone report is specifically requested, other reports will be forwarded by mail. All reports may be obtained by telephoning the laboratory (ARNold 5440).

### EMERGENCY MATERNITY AND INFANT CARE PROGRAM

The Congress of the United States has passed legislation limiting the eligibility of the wives and infants of men in the four lowest pay grades of the armed services under the Emergency Maternity and Infant Care program to June 30, 1947, as follows:

If pregnancy occurs after June 30, 1947, the wife will not be eligible for payment for maternity care, nor will the infant be eligible for care during the first year of life.

All care for mothers and infants authorized on or before June 30, 1947, will be completed.

If pregnancy occurs on or before June 30, 1947, the wife will be eligible for payment for maternity care and her infant will be eligible for care during the first year of life. Applications for care of wives and infants eligible on or before June 30, 1947, may be considered for approval even though the application is submitted after June 30, 1947.

The prompt submission of outstanding medical bills will be appreciated by the Division of Maternal and Child Health, 73 Tremont Street, Boston.

### MISCELLANY

#### CASH SICKNESS BENEFITS FOR RAILROAD WORKERS

A cash sickness-benefit system for railroad workers began to operate throughout the Nation on July 1. These benefits were added under the 1946 amendments to the Railroad Unemployment Insurance Act and provide partial compensation for wage loss due to disability, on the same basis as that due to unemployment. The system is administered by the Railroad Retirement Board.

All disabilities that prevent railroad employees from working, regardless of how or where they occur, are covered

under the program. In the first year of operations, about 300,000 of the 2,075,000 qualified railroad workers are expected to receive benefits, and the total amount of benefits is expected to reach \$36,000,000.

A physician's statement of sickness will be required before claims can be paid. It is believed that the program will require about six hundred and fifty thousand medical examinations a year. Employees are free to choose their own doctors, and any physician to whom an employee goes for examination or treatment may supply the information required as initial proof of an employee's claim.

The forms on which medical information will be requested from a physician are the "Statement of Sickness" and the "Supplemental Doctor's Statement." The first is intended primarily to obtain information at the beginning of each illness, and the second is intended to obtain additional information only when such information is needed later on in the same illness. The statements are designed to furnish, as simply and as conveniently as possible for the physician, the minimum information required for Board purposes.

The "Statement of Sickness" must be mailed to the appropriate regional office of the Railroad Retirement Board within seven days after the first day claimed as a day of sickness, otherwise the employee may lose part of his benefits. Claims for succeeding fourteen-day periods may be allowed for a predetermined period as indicated by the medical evidence on the doctor's initial statement, but in continuing illnesses supplemental information about the patient's illness may also be requested from the physician.

Claims will be filed and adjudicated in the regional offices of the Railroad Retirement Board. These offices are located in Atlanta, New York City, Cleveland, Chicago, Dallas, Kansas City, Minneapolis, Denver and San Francisco and serve the adjoining territories. Each will have a physician who will act as a medical consultant. Additional information about the program may be obtained from any of these regional offices or from district offices. For the New England states, the regional office is in New York City (341 Ninth Avenue), and the district office in Boston (1802 Post Office Building).

## CORRESPONDENCE

### MEDICAL JOURNALS WANTED

*To the Editor* The American Red Cross has been requested by the International Red Cross to assist in securing the following copies of the *American Journal of Medical Sciences*:

February 1946	July 1945	November 1944
January 1945	January 1944	December 1944
March 1945	July 1944	November 1943
April 1945	September 1944	April 1942
June 1945	October 1944	April 1941

The copies are for the Netherlands Red Cross Society, which is desperately trying to help that country rebuild its war-shattered medical services.

The publishers have advised that these missing issues are not available. Those who have any of the above copies and are willing to donate to this worthy cause, are requested to send them to American Red Cross, Boston Metropolitan Chapter, Community Service to Camps and Hospitals, 17 Gloucester Street, Boston 15.

MRS V H KAZANJIAN, *Chairman*  
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## BOOK REVIEWS

*Shock Treatments and Other Somatic Procedures in Psychiatry*  
By Lothar B. Kalinowsky, M.D., and Paul H. Hoch, M.D.  
With a foreword by Nolan D. C. Lewis, M.D. 8°, cloth, 294 pp. New York: Grune and Stratton, 1946. \$4.50.

This is unquestionably a good book and may be considered the latest word on shock therapy. It surveys the history of somatic treatment for mental illnesses, discusses various methods of treatment in some detail and recounts the theories by which various men have tried to explain the success of

shock and convulsive therapy. The material is conscientiously documented. It is presented thoughtfully and yet with a minimum of personal bias—a characteristic that is especially rare among physicians who are practicing particular types of shock therapy.

Persons interested in deep psychology may regard the discussion of psychologic aspects of treatment as a little less than open minded, the hazards complications and in adequacies of organic treatment are thoroughly outlined however, and the empirical nature of these treatments is acknowledged and the advantages (of which there are many) of the somatic approach honestly evaluated.

Drs Kalinowsky and Hoch offer excellent general descriptions of the techniques of the different types of treatment (insulin shock, the convulsive therapies, combined insulin and convulsive treatment, other somatic nonsurgical treatments and prefrontal lobotomy) and the reactions of the patients during and after these treatments are thoroughly described from the physical and social points of view.

The point of the theoretical aim of treatment is left in question at the end of the book but perhaps one should not quibble over this, since expression of personal views was evidently not the entire intention of these authors. A far-minded reader of this book cannot fail to be profoundly grateful that such a comprehensive survey of this important field has been made available in an up-to-date form.

The authors deserve to be congratulated on their well organized and distinguished performance in the writing of this book, as well as on the actual clinical work on which it is based. All this has obviously been a serious and important undertaking to them.

*The Traumatic Deformities and Disabilities of the Upper Extremity.* By Arthur Steindler M.D. In collaboration with John L. Marxer M.D. 4<sup>th</sup> cloth, 494 pp., with 443 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$10.00.

This excellent volume is a sad commentary on the state of the immediate surgery of trauma in this country. At least half the deformities and disabilities it describes should never have been allowed to occur and were the result of ignorance and neglect in primary treatment. Nowhere in the book however is this mentioned. The authors simply review their extensive experience in reconstruction and rehabilitation. Two hundred and sixty pertinent and well illustrated cases are presented. It is refreshing to note that not all these are surgical triumphs. The failures are often much more instructive than the successes. Personal experience is emphasized but the literature is thoroughly reviewed.

Other surgeons will not share the author's enthusiasm for certain procedures such as fascial reconstruction of the dislocated acromioclavicular joint and suspension operations for recurrent dislocation of the shoulder. A discussion of the British and American experiences with peripheral nerve injuries during World War II could have been included to advantage. Descriptions of operative technique are perhaps oversimplified and could encourage the inexperienced to attempt procedures that are often complex and trying in the most expert hands.

But these are minor criticisms and do not detract from the value of the book as a whole. It should be on the shelf of everyone whose practice includes surgery of the extremities.

## BOOKS RECEIVED

The receipt of the following books is acknowledged and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Check and Double Check on Sickness Insurance.* By J. Weston Welch B.S., M.Ed., instructor in economics and business law, Portland (Maine) High School. 8<sup>th</sup> paper, 62 pp. New York: Medical Society of the State of New York, 1946.

Mr. Welch has prepared this pamphlet as a condensation from a large manual on the subject written for debate purposes. It is written in the form of questions and answers and is intended for the use of all persons called on to speak on the subject. It should prove useful for this purpose.

*Medical Social Service in Tuberculosis Control.* Federal Security Agency, United States Public Health Service. 8<sup>th</sup> paper, 22 pp. Washington: Federal Security Agency, 10 cents.

The Tuberculosis Control Division of the United States Public Health Service is formulating a plan for medical social service and to assist in this undertaking an advisory committee of social workers was formed by the American Association of Medical Social Workers in October 1945. This pamphlet comprises the report of the first meeting of this group and defines the functions of the medical social worker as they are related to a tuberculosis-control program.

*Outline of the Spinal Nerves.* By John Favill A.B. M.D. clinical professor of neurology (Rush) University of Illinois College of Medicine and attending neuropsychiatrist, Presbyterian Hospital Chicago. 8<sup>th</sup> cloth, 190 pp. with 24 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$3.75.

Dr. Favill has provided full information on the motor functions of the spinal nerves. The material has been compiled from the recognized standard textbooks of anatomy and where there were disagreements the author made his own choice of data. The material is given in the form of lists, since it has been found that tables are unsatisfactory in the presentation of full data concerning any single nerve or muscle. The text is in five parts: the roots, nerves and muscles, the neurologic aspects of clinical lesions of the muscles with an indication of the etiology of the lesions, the muscles, with their origins, insertions, functions, tests and indications of paralysis, the movements by regions and members showing the muscles and nerves involved and supplementary information concerning the lesions of the plexuses, causalgia, causes of neuritis, neuropathy and low back pain, a description of electrical tests of nerves and muscles and a list of muscular disorders. The volume is written as a companion to the author's manual on the cranial nerves published in 1933. The book is well published in every way except that an important list is printed on the lining of the back cover. Material of this sort should not be printed on the covers of a book since it is damaged or destroyed by handling and lost in rebinding. The manual should prove useful to neurologists and others interested in muscle lesions and should be in all medical libraries as a reference source.

*Quantitative Clinical Chemistry Interpretations.* By John P. Peters M.D. professor of internal medicine, Yale University School of Medicine, and Donald D. Van Slyke Ph.D. Sc.D., member of the Rockefeller Institute for Medical Research. Second edition. Volume I. 8<sup>th</sup> cloth, 1041 pp. Baltimore: Williams and Wilkins Company, 1946. \$7.00.

This standard reference work has been completely rewritten and the wealth of material available has necessitated a rearrangement of the work into three volumes instead of the previous two parts, *Methods* and *Interpretations*. Because of the tremendous progress in recent years in clinical chemistry Dr. Van Slyke has become responsible for the part on methods and Dr. Peters for the part on interpretations. This first volume of *Interpretations* covers the subjects of energy metabolism, chemistry, physiology and clinical complications of the carbohydrates, including diabetes, lipids and protein metabolism. The original objective of the first edition published in 1931 has been adhered to—namely to discuss the substances that are important in clinical medicine and for whose determination suitable quantitative methods are available. A comprehensive bibliography is appended to each part, and all significant original sources are quoted. The bibliography of the lipids alone comprises 979 references. An excellent index concludes the volume. The text is well printed with a good type on light paper resulting in a volume that is not too heavy for its size. This authoritative reference work should be in all medical and hospital libraries and in the libraries of clinicians.

*Progress in Gynecology.* Edited by Joe V. Meigs M.D. clinical professor of gynecology, Harvard Medical School, chief, Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital, surgeon, Pondville Hos-

pital, and gynecologist, Palmer Memorial Hospital, and Somers H. Sturgis, M.D., chief, Vincent Memorial Hospital Laboratory, and assistant surgeon, Massachusetts General Hospital. 8°, cloth, 552 pp., illustrated. New York: Grune and Stratton, 1946. \$7.50.

This composite volume is the work of seventy-one authorities, each writing on a special subject. The objective of the work is to provide the latest knowledge of gynecology for the purpose of refreshing and bringing up to date the men who were with the armed forces. The volume should also prove useful to surgeons, gynecologists and physicians who desire to keep abreast of the times. The material is well organized and arranged in the following divisions: growth and physiology, diagnostic methods, functional disorders, interrelations of endocrine glands, sterility and reproduction, infections and their treatment, benign growths, malignant growths, operative technic and preoperative and postoperative care. A good index completes the volume. The type and printing are good, but the paper is too heavy for the size of the book. The volume is recommended for all medical libraries and the libraries of gynecologists.

*National Formulary.* Prepared by the Committee on National Formulary under the supervision of the Council by the authority of the American Pharmaceutical Association. Eighth edition. Official from April 1, 1947. 8°, cloth, 850 pp. Washington: American Pharmaceutical Association, 1946. \$7.50. (Distributed by the Mack Publishing Company, Easton, Pennsylvania.)

This standard essential reference work has been thoroughly revised and enlarged by the addition of one hundred and eighty-eight new drugs and preparations. Many formulas and standards have been continued in this new edition for *USP XII* drugs not admitted to *USP XIII*. This edition represents the results of four years of planning and work by the committee, the staff of the association's laboratory and hundreds of collaborators. In this edition, for the first time, titles in English precede the Latin titles. The volume maintains the excellence of publication of the previous editions.

*Charles-Édouard Brown-Séquard: A nineteenth century neurologist and endocrinologist.* By J. M. D. Olmsted, M.A. (Oxon), Ph.D., D.Sc., professor of physiology, University of California. 8°, cloth, 253 pp., with two portraits. Baltimore: Johns Hopkins Press, 1946. \$3.50.

This biography of Brown-Séquard, born Charles-Édouard Brown, relates the story of his life in Mauritius, where he was born in 1817, in France, where he received his medical education, in the United States, where he lived for a time, and again in France, where he became a professor at the Collège de France and died in 1894. It contains a wealth of material, but pertinent dates and facts are difficult to find, since they are lost in the narrative. Interwoven with the story of Brown-Séquard's life are commentaries on contemporaries and the relation of their work to that of Brown-Séquard. Despite its difficult style the book should be in all medical-history collections.

*Quarterly Review of Obstetrics and Gynecology.* Volumes I, II and III, 1943-1945, reprinted. 8°, cloth. Washington: Washington Institute of Medicine, 1946. \$25.00 (set).

This set of volumes comprises 2193 pages containing 3663 abstracts of noteworthy articles published in English during 1943-1945. The abstracts are short and contain the essential points of the articles. The publication is excellent in every way. The publisher reprinting these volumes long out of print has made possible their acquisition by interested physicians and specialists. The reprinting was limited to a thousand sets, about two thirds of which had been sold in December, 1946.

*The Essentials of Obstetrics and Gynecology.* By William Albert Scott, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), professor of obstetrics and gynecology, University of Toronto, and H. Brookfield Van Wyck, B.A., M.B., F.R.C.S. (Can.), F.R.C.O.G. (Eng.), assistant professor of obstetrics and gynecology, University of Toronto. 8°, cloth, 390 pp., with 91 illustrations. Philadelphia: Lea and Febiger, 1946. \$5.50.

The authors have based this manual on the course of lectures given to undergraduates in the University of Toronto

Medical School. They have succeeded in condensing the fundamentals of their subjects into a comparatively small volume. The material is well organized. Obstetrics is divided into normal, abnormal and operative. Gynecology is arranged by organs, followed by general subjects and operative procedures. The volume is well published, with a good type, paper and format, and should prove useful as a manual of the subjects.

*Trabajos del Dispensario Antituberculoso Central y del Sanatorio Antituberculoso de Ofra, de Santa Cruz de Tenerife, Canarias (España).* Part VII, 1944-1945. 8°, paper, 336 pp. Santa Cruz de Tenerife: Imprenta Católico, 1946. No charge.

This volume contains a number of papers on the various aspects of tuberculosis, including diagnosis, treatment and association with other diseases. The following subjects are worthy of special notice: the psychopathology of the tuberculous patient, epidemic hepatitis and tuberculosis and a report of an epidemic in a tuberculosis sanatorium with a study of the effect of the hepatitis on the tuberculous patient. The first part is devoted to the statistics of the institution. The volume should be in all large medical libraries and in all special collections on tuberculosis.

*Heparin in the Treatment of Thrombosis.* By J. Erik Jorpes, M.D., reader in biochemistry, Caroline Institute, Stockholm, Sweden. With a foreword by J. R. Learmonth, C.B.C., Ch.M., professor of surgery, University of Edinburgh. Second edition. 8°, cloth, 260 pp., with 21 illustrations, 2 color plates, 1 portrait and 30 tables. New York: Oxford University Press, 1946. \$6.50.

This new edition of a special monograph, first published in 1939, is brought up to date, and the recent experience in the use of heparin in thrombosis and embolism is summarized. The work is divided into two parts: the first considers the chemistry and physiology, including a chapter on dicoumarol; the second is devoted to the use of heparin in the treatment of thrombosis, latent thrombosis and pneumonia and the use of dicoumarol, some aspects of pathogenesis and the social aspects of thrombosis. The text is well documented with statistical tables, and a long bibliography of eighteen pages concludes the volume. The material is well organized and the book is well published in every way except that a heavy coated paper is used when a lighter paper would be more suitable for such a small volume. (Coated and silica-filled papers when wet become as solid as concrete.) The monograph is recommended for all medical libraries and to all physicians interested in vascular diseases.

*The Treatment of Diabetes Mellitus.* By Elliott P. Joslin, M.D., Sc.D., medical director, George F. Baker Clinic, New England Deaconess Hospital, Boston, and consulting physician, Boston City Hospital, Howard F. Root, M.D., physician-in-chief, New England Deaconess Hospital, and associate in medicine, Harvard Medical School, Priscilla White, M.D., physician, New England Deaconess Hospital, and instructor in pediatrics, Tufts College Medical School, Alexander Marble, M.D., physician, New England Deaconess Hospital, and instructor in medicine, Harvard Medical School, and C. Cabell Bailey, M.D., physician, New England Deaconess Hospital, and research fellow in medicine, Harvard Medical School. Eighth edition, thoroughly revised. 8°, cloth, 861 pp., with 13 figures, 117 tables, 1 map and 1 chart. Philadelphia: Lea and Febiger, 1946. \$10.00.

This authoritative treatise is based on the experience of Dr. Joslin and his colleagues over a period of forty-five years, covering the observation of 29,000 patients with diabetes and glycosuria. The text is thoroughly revised, and emphasis placed on statistics, physiology and pathology, as well as treatment. A chapter on alloxan diabetes is included, and the role of this chemical in the causation of diabetes is discussed. The fact that there are one million diabetic patients in the United States makes the disease a major social problem to be faced by the public, the medical profession and the Government. The volume is well published and should be in every medical library and in the libraries of practitioners. It is an outstanding work on an important subject.

(Notices on page xv)

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## RECURRENT CANCER OF THE COLON AND RECTUM\*

### Report of Cases with Favorable Results Following Radical Surgery

J. E. DUNPHY, M.D.†

BOSTON

ADVANCES in the treatment of cancer of the colon and rectum consist largely of measures that have extended the amount of resection.<sup>1-4</sup> In early lesions, such radical surgery offers the best assurance of cure. In advanced lesions, it permits the removal of growths that were formerly regarded as totally inoperable. Even when cancer recurs it can be removed by a second attempt at radical surgery. Once a properly executed resection has been done, however, there is a tendency for the surgeon to believe that the die has been cast. Because most recurrences are beyond the scope of surgery, all recurrences are apt to be considered hopeless. Removal of such lesions is regarded merely as a surgical feat without benefit for the patient. It is the purpose of this paper to point out that this attitude of pessimism is not entirely justified.

It has been proposed that since surgery is the only way to treat cancer of the colon initially it should be employed whenever possible in dealing with recurrences.<sup>2</sup> If there is no positive evidence of distant metastases or generalized peritoneal seeding, reoperation should be considered regardless of the extent of the first operation, the histologic character of the growth or the apparent fixation of the recurrence. The following cases are illustrative of what may be accomplished.

**CASE 1.** A G, a 36-year-old woman, was admitted to the hospital in August, 1936, because of acute intestinal obstruction following abdominal cramps and rectal bleeding of 3 months duration. Laparotomy disclosed a constricting lesion of the sigmoid, producing complete obstruction. A right transverse colectomy was performed. Postoperatively a large pelvic abscess required colpotomy. One month later resection of the sigmoid with end-to-end anastomosis was performed. The convalescence was uneventful and the transverse colectomy was closed 2 weeks later.

Biopsy of the tumor revealed an adenocarcinoma that was moderately rapidly growing; the regional lymph nodes were extensively involved.

The patient re-entered the hospital 18 months later because of crampy abdominal pain of 3 months and rectal bleeding of 2 weeks' duration. There was a large tender

fixed mass in the left lower quadrant and pelvis. It felt like a large ovarian tumor fixed to the lateral wall of the pelvis. At reoperation a solid tumor mass involving the sigmoid, mesentery, retroperitoneal tissue and left adnexa was resected. A permanent colostomy was performed. The rectal stump was closed below the level of the peritoneum.

Pathological examination disclosed a solid mass of adenocarcinoma. No lymph nodes were identified. The growth histologically appeared to be more rapidly growing.

The patient re-entered the hospital 4 years and 5 months later for repair of a ventral hernia. She was asymptomatic. At operation no definite evidence of tumor was found. A small egg sized nodule along the course of the ureter was thought to be a mass of scar tissue. She re-entered the hospital 1 year later with acute intestinal obstruction of 2 weeks duration. She died of peritonitis following a laparotomy for small bowel obstruction due to recurrent cancer.

**Autopsy.** Post mortem examination revealed a solid mass of rapidly growing adenocarcinoma involving the ureter, iliac artery and vein, psoas muscle, the colostomy and many loops of small bowel. There was no tumor in the pelvis and no metastases in the liver.

The total survival after the second operation was 5 years and 5 months—the patient lived for 5 years and 2 months without symptoms.

The significant point about this case is not that a large recurrent tumor mass was arrested for over five years but that had the surgery been slightly more radical, a permanent arrest would have been accomplished. It is also remarkable that four years after the second operation, the recurrent growth was so small that it was not recognized as tumor and yet a year later there was a huge diffuse recurrence, as if for a time the lesion had remained dormant and had suddenly begun to grow again.

**CASE 2.** E. K., a 54-year-old man, was admitted to the hospital in August, 1930, because of anorexia and diarrhea of 6 weeks duration and pain in the right lower quadrant and tenderness and swelling of a 35 year-old appendectomy scar of 3 days duration. There was a large abscess in the right lower quadrant, pointing in the old appendectomy wound although its etiology was not clear. Incision and drainage of the abscess were necessary. Two weeks later a barium enema showed a large filling defect in the cecum. A right colectomy was performed with an end-to-side ileotransverse colostomy (Fig. 1). The tumor had invaded the abdominal wall about the old appendectomy scar. The entire thickness of the parietes was generously excised in this area. Convalescence was uneventful.

Pathological examination disclosed an adenocarcinoma that had extended through and beyond the bowel wall. The regional lymph nodes were extensively involved. Histologically the tumor was growing slowly.

\*Presented at a meeting of the Boston Surgical Society, December 2, 1946.  
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The patient re-entered the hospital  $2\frac{1}{2}$  years later, complaining of pain in the right flank, loss of weight and a lump in the scar. Examination disclosed a large, ill defined mass that appeared to involve the abdominal wall. Some observers thought that it was a mass in the liver.

A large mass involving the abdominal wall and round ligament of the liver was found at the second operation. It was excised en bloc with the tissues of the abdominal wall (Fig 2).



FIGURE 1 Case 2

*This carcinoma of the right colon, involving the abdominal wall, was removed by a right colectomy. Note the abundant mesentery, indicating adequate removal of regional nodes, which were extensively involved.*

The defect in the abdominal wall, which measured 12.5 by 10 cm. was closed by sliding over the left rectus and the right external rectus. Convalescence was uneventful.

Pathological examination revealed a solid mass of adenocarcinoma, no lymph nodes were identified. Histologically the tumor was observed to be invading tissue planes but was growing slowly.

The patient is alive and well without evidence of recurrence  $6\frac{3}{4}$  years since the second operation.

**CASE 3** D. R., a 52-year-old man, was admitted to the hospital in July, 1939, because of rectal bleeding, tenesmus and loss of weight for 18 months. A large fixed mass was palpable in the left lower quadrant. A barium enema showed a filling defect in the sigmoid, with direct extension to the bladder and terminal ileum. A right transverse colostomy and a side-tracking ileocolostomy were performed. Post-operatively, the patient developed a wound infection. Three weeks later resection of the sigmoid, terminal ileum and upper third of the bladder was performed. Convalescence was uneventful. The colostomy was closed 2 weeks later.

Pathological examination disclosed a rapidly growing adenocarcinoma with local extension to the urinary bladder and ileum and many lymph-node metastases.

The patient re-entered the hospital 2 years later because of abdominal cramps and rectal bleeding. There was an ill

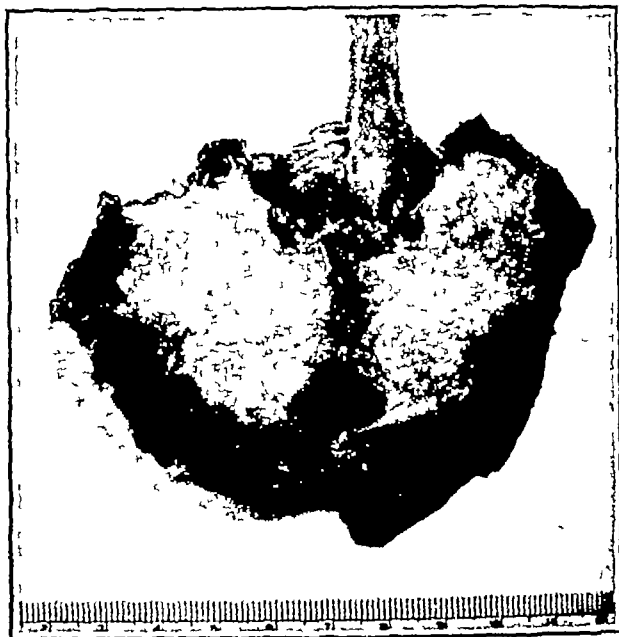


FIGURE 2 Case 2

*This solid mass of recurrent adenocarcinoma, involving the abdominal wall and round ligament of liver, was removed two years after the first operation. The patient is alive and well six years and nine months after the second operation.*

defined mass low in the left lower quadrant just at the base of the pelvis. A barium enema showed evidence of extrinsic



FIGURE 3 Case 4

*This is a solid mass of adenocarcinoma involving the perineum and prostate two years after abdominoperineal resection. The patient was asymptomatic for four years after radical removal.*

pressure on the sigmoid. At operation a mass of solid tumor was found to involve the sigmoid, mesentery, bladder, left ureter and retroperitoneal tissues, it was separated with difficulty from the iliac vessels. The ureter was resected, but because of lateral displacement it was sufficiently long to

permit an end-to-end anastomosis. A permanent colostomy was performed. The serosa over the posterior aspect of the bladder was removed with the tumor, but the bladder wall was not involved. Convalescence was uneventful.

Pathological examination revealed that the tumor was a mass of adenocarcinoma in fat that was involving the bowel wall. Histologically, it was extremely anaplastic with many lymph-node metastases.

The patient is alive and well without evidence of recurrence 5½ years since the second operation. The function of the left kidney is normal.

This was certainly an unfavorable case by ordinary standards. The tumor was rapidly growing, the regional lymph nodes were extensively involved, and the original removal had to include portions of the bladder and ileum. Under such circumstances, the recurrence might well have been viewed as being beyond the scope of surgery. Yet, in retrospect, this has proved to be one of the most successful cases.

**CASE 4.** R. F., a 68-year-old man was admitted to the hospital in February 1940 because of bloody diarrhea of 3 months duration. Examination showed a large slightly fixed tumor in the left posterior wall of the rectum extending to within 2.5 cm. of the rectum. It was removed in one stage by an abdominoperineal resection. Convalescence was complicated by acute cystitis and an abscess in the posterior wound.

Pathological examination disclosed a slowly growing adenocarcinoma without lymph node metastases.

Eight months after operation a perineal recurrence was noted. Operation was not considered feasible. The perineal mass, however, increased in size, became painful and bled occasionally. The patient re-entered the hospital 22 months after the original operation. A radical perineal excision of the tumor, together with a total prostatectomy was performed (Fig. 3). Convalescence was uneventful except for urinary incontinence.

Pathological examination revealed a solid mass of adenocarcinoma; histologically, the tumor appeared to be more rapidly growing.

The patient remained symptomatic for 4 years, although after 2 years there was evidence of a recurrence in the perineum for which he refused hospitalization. At present 5 years after operation he is bedridden with recurrent cancer.

The significant point in this case is again not the palliation of four years' duration but the fact that had reoperation been carried out sooner, an even more favorable result might have been obtained.

These cases have been selected as examples of what may be accomplished by a second attempt at extirpation of carcinomas of the colon and rectum that have recurred locally. Obviously, if there are distant metastases or generalized peritoneal seeding, such surgery should not be attempted. The results in these cases, however, suggest that a tumor that recurs locally without distant metastases is peculiarly amenable to surgery if it can be completely eradicated.

A review of the histology of the tumors in these cases provided no clue to why distant metastases had not occurred. There were extensive lymph-node metastases in Cases 1, 2 and 3, and in Cases 1 and 4 there was evidence of blood-vessel invasion. Nor was the rate of growth of the tumor a reliable guide to prognosis in the individual case. None of the tumors were exceedingly anaplastic, but in Cases 1 and 3 there was moderately rapid growth. Cases 2 and 4 were more slowly growing, but in Case 2 there was lymph-node involvement and in Case 4 there was blood-vessel invasion. In the present state of knowledge the histologic character of the original growth seems to constitute no reason for withholding surgery if the tumor recurs.

The possible role of inflammation in limiting the distant spread of these tumors occasions comment—in Cases 1, 2 and 4 there were local abscesses in and around the growth, and in Case 3 the tumor was of an extremely inflammatory character. A study of the histology of the tumors, however, provided no evidence to support this notion. Whether or not an inflammatory reaction sealed off the lymphatic vessels at the base of the mesentery is a problem for pure speculation and future observation.

The principal point to be stressed is that one must not give up in dealing with cancer.

### CONCLUSIONS

Recurrent cancer of the colon and rectum is not necessarily hopeless.

Tumors that grossly and histologically appear unfavorable may recur locally without distant metastases.

If there is no positive evidence of distant metastases or generalized peritoneal seeding, reoperation should be considered in the treatment of recurrent cancer of the colon, regardless of size and apparent fixation.

Gratifyingly long periods of arrest may follow such operations.

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## INFECTIOUS HEPATITIS ASSOCIATED WITH PREGNANCY\*

## A Report of Four Cases

RALF MARTIN, M D,† AND FRANK C FERGUSON, JR, M D ‡

PORTLAND, MAINE

**A**N EPIDEMIC of infectious hepatitis began among the civilian population of Portland, Maine, during 1944, and has continued to date. Four cases occurred in pregnant women. Since this combination is rare, having occurred in only 10 of 72,000 pregnant patients at the Chicago Lying-in hospital,<sup>1</sup> the cases reported below are presented in detail.

The sedimentation rates mentioned in these cases were determined by the Wintrobe method, corrected for anemia, with normal results in women of up to 20 mm in 1 hour. Normal values for the icteric index were 4 to 7 units per cubic centimeter. In the bromsulfalein test 5 mg of dye per kilogram of body weight was employed, and 0 to 5 per cent retention of the dye in 30 minutes was considered normal. All hippuric acid excretion tests were based on the oral administration of 6 gm of sodium benzoate, the excretion of 3 gm of hippuric acid being regarded as 100 per cent, values as low as 80 per cent were considered normal.

**CASE 1** A 26-year-old multipara, who had been followed in the hospital since the age of 10 for cretinism, secondary anemia and multiple nephrolithiasis, was admitted to the hospital on January 11, 1945. There had been no change in the kidney stones during recent years. The cretinism had been well controlled by desiccated thyroid and was stable, giving no problems during the interval covered by this report. The patient admitted a single sexual exposure in August, 1944, although she claimed continuation of the menses up to the time of admission. The expected delivery date was some time in May. On about December 11 she had suddenly developed anorexia, nausea, severe vomiting, constipation, lethargy, low-back pain, photophobia, excessive lacrimation and frontal headaches. Several days later she noted dark urine, light stools and the appearance of jaundice. A vaginal discharge also developed. All the symptoms disappeared after approximately 1 week, but the jaundice continued to be intense. There was no history of contact with infectious hepatitis.

Physical examination revealed deep jaundice, marked sluggishness, a uterus enlarged to the umbilicus and numerous vaginal polyps (identified by biopsy as condylomata acuminata). The liver and spleen were not palpated, and the temperature was normal.

Examination of the blood disclosed a red-cell count of 3,200,000, with a hemoglobin of 9.3 gm, and a white-cell count of 6500, with 30 per cent lymphocytes. The icteric index was 50, and there was an immediate direct van den Bergh reaction. Examination of the urine showed large amounts of bile and slightly increased amounts of urobilinogen. Blood Kahn and Hinton tests were negative. The hippuric acid excretion was 0. The principal tests by which the patient's course was followed are presented in Table 1.

Initial therapy consisted of a light diet, a single infusion of physiologic saline solution, complete bed rest and continued oral administration of desiccated thyroid, the dosage being adjusted from time to time on the basis of basal metabolic rates.

On January 15 a special diet, consisting of 150 gm of protein, 80 gm of fat and 200 gm of carbohydrate was begun, supplemented by 50 gm of casein hydrolysate (in the form of 1000 cc of Amigen solution) and 100 gm of glucose (as 1000 cc of 10 per cent glucose solution in distilled water) intravenously daily; 5 cc of crude liver extract and various synthetic components of the vitamin B complex were given intramuscularly daily and 20 gm of brewer's yeast with 60 cc of crude liver extract by mouth daily. Additional tests of liver function revealed the prothrombin time to be normal, the total protein was 5.1 gm per 100 cc, with 3.1 gm of albumin and 2.0 gm of globulin, and a quantitative indirect van den Bergh test showed increased amounts of hemobilirubin. An oral glucose-tolerance test on January 22 was normal.

There was a gradual fall in the icteric index and a diminution in the clinical signs of jaundice, although the sedimentation rate was unchanged. On February 5 the patient insisted on getting up daily, and the therapy was discontinued because of nausea and vomiting, which the patient attributed to the treatment. The appetite continued poor, so that little of the diet was actually taken. On February 8 and 10 she was given transfusions of 500 cc of blood, since the red-cell count and hemoglobin had fallen. Four days later the Amigen was resumed intravenously, with vitamin supplements and liver extract by mouth. The clinical condition and laboratory tests failed to improve further, and on March 2 a tender liver was palpated below the costal margin. With the lack of improvement, all treatment was stopped on March 5 for a period of observation, the bromsulfalein retention increased, the hippuric acid excretion further decreased, and the liver remained enlarged and tender. A glucose-tolerance test 10 days later showed a definite reduction in tolerance. There was constant anorexia and nausea, with vomiting that was occasionally severe enough to produce marked acetoneuria. Under these circumstances it was deemed necessary to terminate the pregnancy. On March 24 a cesarean section was performed under spinal anesthesia. The umbilical cord was green, and the amniotic fluid yellow, but the baby appeared normal. Seven days later the baby died. Autopsy showed no disease related to the maternal hepatitis, and death was attributed to atelectasis from aspirated gastric contents, pulmonary congestion and prematurity. The child's liver appeared normal.

Following the cesarean section the mother was given another transfusion and was again confined to bed. For several days she ran a high temperature, whose cause was never determined. Several blood cultures were negative. The temperature eventually returned to normal, and a steady improvement in the liver function tests, with a slow clinical improvement, began. On April 9 the patient was again allowed up. On April 23 she received another transfusion, and the glucose-tolerance test was normal. Clinical jaundice disappeared on April 30, but the liver was still enlarged. In an attempt to speed resolution of the enlargement the intravenous casein hydrolysate and intramuscular liver extract were resumed on May 7. On that day the total blood protein was 6.1 gm per 100 cc, with an albumin of 4.4 gm and a globulin of 1.7 gm. Treatment was stopped on May 17, which was the last day on which the liver was palpable. Two more transfusions were subsequently given. Finally, on May 26, being in excellent condition, the patient was discharged.

Subsequent visits showed continued well being, and the anemia improved, although the blood counts were still not within normal limits. On the last visit—in February, 1946—the blood sugar was 80 mg, and the total blood protein 6.3 gm per 100 cc. There was a change in the albumin-globulin ratio; however, the former being 3.1 gm and the latter 3.2 gm.

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This patient contracted infectious hepatitis in the second trimester of pregnancy. Intense jaundice persisted, and there was evidence of liver damage. Following the start of therapy, there was some improvement over two months. When treatment was stopped there was evidence of further deterioration, and it was decided to interrupt the pregnancy. Cesarean section was performed at about the seventh month. The baby died from causes probably not associated with the hepatitis. After the section there was clinical and chemical improvement, which cannot be attributed specifically to any therapy given. Seven and a half months after discharge, there was still an elevated sedimentation rate and altered blood protein, some permanent liver damage presumably being indicated. The total period of jaundice was approximately one hundred and thirty days.

**CASE 2.** A 26-year-old woman who had had five previous normal pregnancies and births was admitted to the hospital on April 27, 1945. She had been seen in the hospital in 1943 for bronchiectasis and empyema. The last menstrual period had begun in October 1944 and delivery was expected in July 1945. The pregnancy had been uneventful until April 22, when fever, low back ache, nausea, vomiting, anorexia and constipation had gradually begun. There was no history of contact with infectious hepatitis.

Physical examination showed a moderately ill patient, with a normal intrauterine pregnancy, coarse rales in both upper-lung fields, tenderness in the right upper quadrant of the abdomen and left costovertebral tenderness. She was treated with complete bed rest, a diet of soft foods and an occasional infusion when the vomiting was marked. Examination of the urine disclosed bile, albumin, sugar and casts.

On the next day clinical evidence of jaundice appeared; the sedimentation rate was 42 mm., and the icteric index 25 with an immediate direct van den Bergh reaction. The fever was of low grade; the temperature never exceeding 100°F. by mouth and together with most symptoms had disappeared by April 29. An x-ray film of the chest showed the same degree of fibrosis as previously, a urine culture was negative, and blood Kahn and Hinton tests were negative. Symptomatically the patient was well and since there were no clinical signs, she was followed solely by laboratory tests.

On April 30 the icteric index had risen to 40, the white-cell count was 7300 and the urine still showed bile, albumin and sugar. On May 1 the sedimentation rate was 32 mm. in 1 hour and the icteric index 52, and the bromsulfalein test showed 80 per cent retention of the dye. The diet was changed to 175 gm. of protein, 80 gm. of fat and 225 gm. of carbohydrate with about 15 gm. of brewers' yeast daily. On May 7 the icteric index was still 50, the sedimentation rate had risen again to 33 mm. in 1 hour, the total blood protein was 6.4 gm. per 100 cc., with 3.0 gm. of albumin and 3.4 gm. of globulin, and the stools were still clay colored. It was decided to reinforce the daily diet with 5 cc. of crude liver extract intramuscularly and 50 gm. of casein hydrolysate intravenously. At first these infusions gave many febrile reactions and further decreased the appetite but tolerance to them gradually improved.

On the morning of May 9 the patient passed blood clots by vagina and labor pains started. An easy delivery was performed 4 hours later. The pregnancy had thus progressed to approximately 6½ months. The child weighed 3 pounds 10½ ounces but appeared well. The baby was kept in the hospital until June 18, when the weight was 5 pounds, 3 ounces and it was discharged in excellent condition.

Following delivery the patient was put on a regular diet but the Amigen, brewers' yeast and liver extract were continued. On May 10 the sedimentation rate was 50 mm. in 1 hour, and the icteric index was 50. Thereafter she began to improve. On May 15 urobilin reappeared in the stools, the icteric index was 25, the blood cholesterol 214 mg. per 100 cc., and the sedimentation rate 46 mm. in 1 hour. Four

days later a hippuric acid test showed 30 per cent excretion but the bromsulfalein test revealed only 15 per cent retention of the dye. The icteric index was 20 on May 21 and 15 on May 24 and 31, by which time the sedimentation rate was 44 mm. in 1 hour, bilirubin had disappeared and the cholesterol was 188 mg. per 100 cc. On June 5 the icteric index was 10, and the sedimentation rate 44 mm. in 1 hour and the bromsulfalein test showed 15 per cent retention of the dye. The patient was then allowed up for the first time. Three days later the icteric index was 10, the sedimentation rate was 43

TABLE 1 Results of Liver-Function Tests in Case 1

Date	Icteric Index	Sedimentation Rate mm./hr.	Hippuric Acid Excretion %	Bromsul- falein Re- tention %	Takata- sawa Test
January 13	50	42	0	—	Positive
19	60	41	—	—	—
21	60	41	—	—	—
27	25	39	—	—	—
30	25	41	—	—	—
February 5	20	37	—	—	—
10	—	45	—	—	—
14	20	—	20	10	Positive
19	50	—	—	—	—
20	20	44	—	—	—
26	25	25	—	—	—
March 2	20	41	17	—	—
6	20	38	—	—	—
19	20	40	—	25	—
24*	—	35	9	50	Positive
25	25	35	—	—	—
27	—	—	—	70	—
April 10	20	44	13	10	Positive
14	—	—	30	—	—
27	—	41	—	50	—
30	15	—	—	—	—
May 5	—	—	—	25	—
7	10	43	—	—	Positive
11	7	41	65	5	—
18	7	44	53	5	Question- able
24	7	50	—	—	—
26†	—	—	—	—	—
June 12	5	43	—	—	—
July 17	—	41	—	—	—
February 1	5	34	—	—	Negative

\*Cesarean section performed on this date.

†Patient discharged.

mm. in 1 hour and the bromsulfalein test showed 10 per cent retention of the dye. The casein infusions, yeast and liver extract were discontinued. June 12 the liver function tests were normal—the hippuric acid test was 82 per cent and the bromsulfalein test showed 5 per cent retention of the dye, the icteric index was 10 and the sedimentation rate 47 mm. in 1 hour.

The patient was discharged on June 14 on a high-carbohydrate, high-protein diet. Two weeks later the icteric index was 5 and the sedimentation rate 31 mm. in 1 hour. She did not return for further follow up study.

This patient contracted hepatitis late in the second trimester of pregnancy, showed definite evidence of liver dysfunction, and was delivered at six and a half months of a normal baby who lived. Improvement began soon after delivery. Before discharge the patient showed a complete clinical recovery, all laboratory tests having returned to normal except for a high sedimentation rate. She did not return for follow-up studies, so that no statement can be made regarding permanent liver damage, although it seems unlikely. The jaundice lasted approximately thirty days.

**CASE 3.** A 24-year-old woman who had had a previous normal pregnancy was admitted to the hospital on May 23,

1945, with the complaint of jaundice. The last menstrual period had begun on December 1, and the expected date of confinement was September 7. On March 18 a dead but otherwise apparently normal fetus had been delivered at another hospital. On April 18 the patient had noted the gradual onset of nausea, vomiting, diarrhea and fever. There had been no known contact with hepatitis. Several days later the stools had become light in color, and the urine dark. Jaundice had then developed. She had not limited her activities or sought medical advice. The fever and symptoms had gradually disappeared, but the jaundice had become intenser and had shown no signs of remission.

Physical examination showed only the jaundice and a low-grade fever, the temperature never exceeding 100°F by mouth. Examination of the blood disclosed a white-cell count of 5500, with 37 per cent lymphocytes. The icteric index was 100, with an immediate direct van den Bergh reaction, the sedimentation rate was 5 mm in 1 hour, a bromsulfalein test showed 100 per cent retention of the dye, the blood cholesterol was 137 mg per 100 cc, and blood Kahn and Hinton tests were negative. Examination of the urine disclosed heavy amounts of bile with traces of sugar. The stools were definitely light in color.

The patient was immediately put on complete bed rest and started on a high-protein diet. On May 25 daily administration of 1000 cc of Amigen solution intravenously, 10 gm of yeast and vitamin supplements by mouth and 5 cc of crude liver extract intramuscularly was begun. Because of the poor condition of the veins, it was not always possible to give the daily infusion. The fever soon disappeared, and since the patient had no symptoms or physical signs, the course was followed solely by the laboratory tests.

On May 31 the icteric index had risen to 150, the sedimentation rate was 10 mm in 1 hour, the bromsulfalein retention was still complete, and a Takata-Ara flocculation test was negative. On June 5 there was no fundamental change, the icteric index being 100 and the sedimentation rate 21 mm in 1 hour. A week later the icteric index was the same, the cholesterol was 188 mg, and the blood protein 6.1 gm per 100 cc, with 4.4 gm of albumin and 1.7 gm of globulin. On June 18 the icteric index fell below the admission level for the first time, being 75, and the sedimentation rate was 18 mm in 1 hour. Amigen infusions were discontinued after 30 days. On June 26 and July 3 the icteric index was the same, there was still an immediate direct van den Bergh reaction and a sedimentation rate of 20 mm in 1 hour, but on the latter date the bromsulfalein test showed 40 per cent retention of the dye. On that day the patient was allowed up for the first time. The yeast, vitamins and liver extract were continued. A week later the icteric index was 50. She went home July 13 and probably took no medications or diet. The jaundice, however, disappeared soon after discharge.

The icteric index was 15 on July 18 and 10 on August 1, when the bromsulfalein test showed 15 per cent retention of the dye. Further bromsulfalein tests showed 20 per cent retention on September 13, none on October 24 and none on January 4, 1946.

This case might strictly be excluded from the series, since symptoms of hepatitis first appeared about thirty-one days after a miscarriage, occurring at the end of the first trimester. Since Havens<sup>2</sup> has stated that the incubation period is from twenty to forty days, however, it is evident that infection occurred at about the time of, or perhaps even before, the miscarriage. Whether the hepatitis was directly related to the miscarriage cannot, of course, be determined. After a month of jaundice, therapy was started. Although treatment was not so intensive as we should have wished, some improvement began about three weeks after admission and continued until no evidence of liver damage was apparent. The total duration of jaundice was eighty to eighty-five days.

**CASE 4** A 39-year-old woman who had had a tubal pregnancy in 1932 and five subsequent normal pregnancies was admitted to the hospital on June 1, 1945, acutely ill. The last menstrual period had begun on November 23, and the expected date of delivery was August 30. On May 30 she had had a shaking chill and had rapidly developed fever, sweating, headache, nausea, vomiting, severe pains in the lower back and lower abdomen and pain on moving the eyes.

Physical examination showed only a normal intrauterine pregnancy. On the next day examination of the blood revealed a red-cell count of 3,300,000, with a hemoglobin of 11 gm, and a white-cell count of 3200, with 15 per cent lymphocytes. The icteric index was 5, and a bromsulfalein test showed 70 per cent retention of the dye. The urine was normal. No history of contact with hepatitis could be obtained.

The symptoms and a low-grade fever persisted until June 4, when clay-colored stools and biliruria developed. On the following day jaundice appeared. On June 6 the icteric index was 50 with an immediate direct van den Bergh reaction, and the sedimentation rate was 18 mm in 1 hour. Treatment consisted of complete bed rest, codeine for the headache and backache and 2000 to 3000 cc of 10 per cent glucose solution in distilled water by vein daily. By June 8 the patient felt well enough to start on a normal diet, the codeine and infusions being discontinued. On the next day the icteric index was still 50, and the sedimentation rate had risen to 32 mm in 1 hour. On June 11 an enlarged tender liver was palpated. An oral glucose-tolerance test was normal on the following day. On June 15 the bromsulfalein test disclosed 40 per cent retention of the dye, a quantitative indirect van den Bergh test showed 5 mg of hemobilirubin per 100 cc., and the sedimentation rate was 46 mm in 1 hour. Eight days later the icteric index was 15, and the sedimentation rate 37 mm in 1 hour, and the bromsulfalein test revealed 20 per cent retention of the dye. The liver gradually diminished in size until June 27, when it could no longer be felt, all jaundice had gone, the icteric index was down to 10, the bromsulfalein retention was only 5 per cent, and the sedimentation rate was 27 mm in 1 hour. The patient was allowed up on that day. On July 2 the icterus was the same, and the sedimentation rate 38 mm in 1 hour. She was discharged two days later.

The patient was not seen again until September 13, when she entered the hospital and spontaneously delivered a normal child. Unfortunately, no liver-function tests were done at that time. The hospital course was uneventful for both the mother and the child.

Four months later the patient was in perfect health, and the liver could not be palpated. The icteric index was 7.5, a van den Bergh test gave no reaction, the sedimentation rate was 9 mm in 1 hour, the Takata-Ara reaction was negative, and a bromsulfalein test showed no retention of the dye.

There is remarkably little in the literature on the concurrence of infectious hepatitis and pregnancy, to which Beck<sup>3</sup> refers as catarrhal jaundice, a condition that is seldom seen in pregnancy. De Lee<sup>1</sup> states that pregnant women show a high mortality in hepatitis. Stander<sup>4</sup> considered "the catarrhal variety" of jaundice in pregnancy to be without significance and to undergo spontaneous cure, but subsequently referred to "epidemics of jaundice in which the disease was disastrous in pregnancy."<sup>5</sup> In the latter report there were many maternal deaths, abortions and premature deliveries.

Saurer<sup>6</sup> reported 5 cases of hepatitis in pregnant women occurring during 1942 and 1943. Four were multiparas ranging in age from twenty-four to thirty-seven years. One had a premature delivery at five months and later developed symptoms of hepatitis, as in Case 3 above. This was apparently the only premature delivery. There were no maternal deaths and no other fetal deaths. Only one

woman, who had delivered at term during the preicteric stage of hepatitis, had a prolonged period of jaundice. In this case the jaundice lasted about three months.

It is impossible to draw definite conclusions from our small series of cases. There were no maternal deaths, and the 2 deaths in the children could be attributed only to the prematurity, not to the maternal hepatitis. In only one woman, however, did both the pregnancy and the hepatitis pursue normal courses. Two patients had premature labors, 1 required termination of the pregnancy, and 2 had prolonged periods of jaundice. The patient in Case 1 may have suffered permanent liver damage, since when last seen she still had an elevated sedimentation rate and an abnormal blood protein level. Permanent damage seems definitely ruled out in Case 4 and unlikely in the other 2 cases.

It seems safe to conclude that the danger of maternal death from hepatitis is small. The chance of an uneventful pregnancy is poor, however, and the possibility of prolonged jaundice and perhaps permanent liver damage in the mother is present. Since improvement in the mother occurred soon after the cesarean section in Case 1 and soon after delivery in Case 2, it appears that the mother benefits from removal of the fetus. Pregnancy itself may place an extra strain on an already diseased liver, and in severe cases of hepatitis interruption of the pregnancy should be seriously considered unless the patient improves rapidly under observation.

Little other treatment will benefit, since therapy in infectious hepatitis has always been purely symptomatic. Recent work by Gellis et al.<sup>7</sup> and by Stokes and Neefe<sup>8</sup> has proved the value of the early prophylactic use of gamma globulin, but the therapy is of no apparent value once symptoms have developed. It might be wise to give a prophylactic dose immediately to every pregnant woman exposed to hepatitis. The difficulty, however, is that in most cases, as in all those presented above, there is no history of known exposure. In the absence of such a history, prompt hospitalization, with complete bed rest, is recommended as soon as the diagnosis of infectious hepatitis is made or suspected in a pregnant woman. Of all the therapy used, bed rest is probably the most important factor. Proof for this statement is not apparent in these 4 cases, but in a large series of uncomplicated cases of hepatitis the duration of jaundice was found to be inversely proportional to the amount of strict bed rest instituted at the onset of the disease, being 40 per cent less in patients hospitalized early than in those whose activity had not been restricted. The 2 patients in this series who were put to bed during the preicteric stage of the disease were jaundiced for only twenty-one and thirty days, respectively,

whereas the other 2, who did not limit their activity, were icteric for eighty and one hundred and thirty days, respectively.

The remainder of the treatment fundamentally consisted in furnishing large amounts of protein, carbohydrate and vitamins in the diet, while limiting the amount of fat. Because of the marked gastrointestinal symptoms the diet was often poorly taken and was therefore supplemented with infusions of glucose and casein hydrolysate, liver extract intramuscularly and yeast and vitamin supplements by mouth. Variations of this therapy were used in 3 cases, with indefinite results. Case 1, after jaundice for a month, showed improvement starting after about two weeks of this treatment. The improvement, however, was not complete since the liver became enlarged, although when treatment was stopped liver function was further impaired. In Case 2 delivery occurred a few days after this regime had been instituted, so that the rapid improvement thereafter may be attributed to either factor. One patient (Case 3) had been jaundiced for a month and began to improve after three weeks of this routine, going on to complete recovery.

From our limited experience, we suggest that gamma globulin be promptly given to a pregnant woman exposed to hepatitis, or if an epidemic has started. Otherwise, the patient should be hospitalized immediately when symptoms develop and given complete bed rest. Then, if the jaundice does not diminish within a few weeks or if the patient had already been jaundiced for some time before hospitalization, the above regime is recommended.

#### SUMMARY

Four cases of infectious hepatitis occurring in pregnant women are described. Two women had premature deliveries, and a third required interruption of the pregnancy. Two women had markedly prolonged periods of jaundice that in 1 resulted perhaps in permanent liver damage.

A suggested outline for management of such cases is presented.

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## MECKEL'S DIVERTICULUM\*

## Report of Two Unusual Cases

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**A**LTHOUGH Meckel<sup>1</sup> is usually credited with the first descriptions of the diverticulum in 1812, Hildanus<sup>2</sup> first mentioned the lesion in 1598, Lavater<sup>3</sup> described it again forty years before Meckel, and Ruysch<sup>4</sup> presented a complete description in 1701. Deneke<sup>5</sup> reported the first clinical case of ulcer in the diverticulum. Deetz<sup>6</sup> originally demonstrated gastric tissue in the mucosa. Heterotopic pancreatic tissue was first noted by Zenker.<sup>7</sup> Womack<sup>8</sup> credits Tillmans with the first demonstration of hydrochloric acid secretion by the gastric glands in the diverticulum.

*Incidence*

The incidence of Meckel's diverticulum is generally accepted to be in the neighborhood of 2 per cent of the population, an estimate concurred in by Nygaard and Walters,<sup>9</sup> Skinner and Walters,<sup>10</sup> Gray,<sup>11</sup> Abt and Strauss,<sup>12</sup> Chaffin,<sup>13</sup> Osler<sup>14</sup> and Turner.<sup>15</sup> Other estimates include that of Ladd<sup>16</sup> (2 to 4 per cent), that of Matt and Timponi<sup>17</sup> (1.5 to 3.0 per cent) and that of Christie<sup>18</sup> (1.1 per cent).

There is consistent agreement among authors that the lesion is a cause of clinical disease in from 15 to 25 per cent of patients in whom it occurs.<sup>1, 9, 18-21</sup> Since this estimate implies that approximately 1 person in each 200 of the general population would be so afflicted, there seems reason to believe that the estimate is too high. During the past five years at this hospital there have been 26 known cases of lesions of the diverticulum, 631 cases of appendicitis having been seen in the same period. Thus, our experience demonstrates that appendicitis is twenty-five times more frequent.

*Anatomy*

The origin of the pouch is the failure of closure of the omphalomesenteric duct, which normally occurs by the seventh fetal week. The sac is usually found on the antimesenteric border of the ileum and rarely between the leaves of the mesentery. It has been found, however, arising from all parts of the intestinal canal from the cardia of the stomach to the rectum. The distance separating it from the ileocecal valve is usually 30 to 90 cm. The sac is often under 10 cm in length and averages about the size of a finger. There have been several

reports of "giant" forms, the largest being that described by Tisdall,<sup>22</sup> which was over 100 cm long, that of Chaffin,<sup>13</sup> which was 96 cm long, that of Moll,<sup>23</sup> which was 85 cm long, and that of Goldstein,<sup>24</sup> which was 66 cm long.

*Pathology*

Anatomic derangements of the structure that may occur are classified by Thompson<sup>25</sup> as follows: antimesenteric, with closed distal end, 82.5 per cent, partial obliteration, with a fibrous cord running to the umbilicus, 10 per cent, umbilical fistula, 6 per cent, "giant" forms, 5 per cent, umbilical polyp, 0.5 per cent, and simple intramesenteric, 0.5 per cent.

Sibley<sup>26</sup> has listed the following structural peculiarities of the lesion: persistence of lumen in the vitelline duct resulting in fistula to the umbilicus, obliteration of the lumen of the cord, with attachment of the cord to the navel, to other viscera or without attachment, cyst formation in the cord, the cyst being either central or distal, with formation of an umbilical sinus, formation of a blind, free-lying pouch — the usual variety, a "daughter" diverticulum arising from the original sac, a blind pouch lying between the leaves of the mesentery, and segmental obliteration, but with persistence of mucosa-lined duct in other areas, communicating with the navel or other viscera.

The study of heterotopic tissue in the diverticulum is one of the most interesting pathologic features encountered. This sac is easily the most frequent site for observance of heterotopic tissue, the incidence of the phenomenon being 34.9 per cent in a total of 1044 cases reviewed<sup>17, 27-36</sup> and the type of tissue noted being gastric, duodenal and jejunal mucosa, pancreatic tissue and biliary duct.

At present there are three theories in explanation of the presence of heterotopic tissue in the diverticulum. The Albrecht<sup>37</sup> theory holds that the sac contains primitive endoderm that can reproduce any cells of the gastrointestinal tract, in contrast to the Schaetz<sup>31</sup> theory, which explains the ectopic cells by implantation during rotation of the gut. Greenblatt<sup>21</sup> favors the "dysembryoma" theory, which considers the diverticulum as a primitive digestive tract and accounts for the heterotopic cells by their failure to undergo involution, a view adhered to by Farr and Penke.<sup>32</sup>

Of the multiplicity of types observed, only the gastric cells are encountered with any frequency;

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and only they have any apparent clinical significance, owing to their ability to form peptic ulcers in the contiguous tissues. Schaafi<sup>28</sup> analyzed the fluid formed by such a diverticulum and demonstrated a free hydrochloric acidity of 40° and a total acidity of 70°. Dragstedt,<sup>29</sup> Lindau and Wulff<sup>30</sup> and Matthews and Dragstedt<sup>31</sup> have shown that this lesion is analogous to the peptic ulcer of the upper intestinal tract, representing a lack of resistance of ileal mucosa to acid contact. It is of interest that the ulcer occurs, not in the patch of gastric cells, but usually in the junction zone of gastric and ileal tissue, often growing to an appreciable extent along the ileal mucosa.

The clinical syndromes that may occur as a result of a lesion in the diverticulum have been classified by Greenblatt and his associates<sup>21</sup> as follows:

The peptic group, a common feature of which is the presence of heterotopic gastric mucosa in the sac, which may or may not cause a peptic ulcer that may in turn cause intestinal hemorrhage or peritonitis by perforation. The patient may thus present the clinical picture of a simple duodenal ulcer, melena, hematemesis or peritonitis.

The obstructive group, in which the pouch is the focus of intussusception, a volvulus, the contents of an inguinal or femoral hernia (Littre's hernia), or the cause of bands and adhesions. The clinical picture is then one of complete or incomplete, acute or chronic intestinal obstruction.

The diverticular group, in which the sac is subject to acute or chronic inflammation, with the possibility of gangrenous change, and in which the symptomatology is essentially that of appendicitis.

The umbilical group, presenting as a fecal fistula, umbilical adenoma or prolapse of intestine through an umbilical fistula.

The tumor group, either benign (enterocystoma, carcinoid, adenoma or mesodermal tumor) or malignant (carcinoma or sarcoma).

The incidental group, in which the lesion occurs without symptoms.

#### Complications and Symptoms

A collective review of the cases reported and reviewed by forty-three authors reveals various complications reported among 1605 cases (Table 1).

The most frequent complication encountered is hemorrhage from the diverticulum, which invariably results from either peptic ulceration or neoplasm. The complication is two to five times as common in boys as in girls,<sup>29, 30, 32-35</sup> and is usually seen in the group from ten to twenty years of age,<sup>17, 74</sup> per cent of cases occurring under the age of fifteen years,<sup>18</sup> but has been encountered at operation in an age span from two weeks to seventy-seven years.<sup>21</sup>

The bleeding may be slight, periodic or intermittent or sudden and profuse, the blood is usually dark rather than either bright or tarry. If the hemorrhage is associated with pain, the distress is usually umbilical in location and may be accentuated, but not relieved, by food.<sup>2</sup> Matt and Timponi<sup>17</sup> state that there are usually long intervals separating episodes of massive melena, which may continue into adult life, and that such a history is almost pathognomonic of a diverticular ulcer. The differential diagnosis includes intussusception (as indicated by "raspberry jam" stools with obstructive symp-

TABLE 1 Complications Observed in 1605 Cases of Meckel's Diverticulum

COMPLICATION	NO OF CASES	PERCENTAGE
Hemorrhage	496	30.9
Intestinal obstruction	383	23.8
Intussusception	176	10.9
Volvulus	16	1.0
Other forms	191	11.9
Perforation	222	13.8
Littre's hernia	188	11.7
Simple diverticulitis	165	10.3
Umbilical fistula	36	2.2
Foreign body	32	2.0
Umbilical polyp	28	1.8
Carcinoma	24	1.5
Tuberculosis	10	0.62
Typhoid perforation	9	0.56
Prolapse through navel	6	0.37
Omphalocele	3	0.18
Traumatic perforation	3	0.18

toms), Henoch's purpura (on the basis of purpuric spots and studies of platelet counts, clot retraction, and clotting and bleeding times), peptic ulcer (as suggested by the patient's age, epigastric pain, response to alkalis and barium studies), colonic and rectal polyps (as indicated by tenesmus, proctoscopy and barium enema), rectal varicosities (visible on proctoscopy) and congenital intestinal telangiectasis. Brenneman<sup>47</sup> has observed that the rectal blood from a Meckel's diverticulum usually contains clots, whereas that formed by an intussusception or an ileocolitis usually does not.

Intestinal obstruction, which is second to hemorrhage in frequency as a complication, generally results from intussusception, with the pouch forming the head of the advancing loop, from volvulus, from bands and adhesions arising from previous inflammatory changes around the sac or from congenital attachments. According to Harkins,<sup>48</sup> intussusception accounts for 17 per cent of the complications arising in Meckel's diverticulum. Precise diagnosis of the cause of the obstruction prior to operation in such cases is manifestly impossible, unless the characteristic antecedent history is present.

Perforation is the third most frequent complication mentioned in the literature and may result from either perforation of a peptic ulcer or advanced diverticulitis. Unless there has been a



history of melena, it will be impossible to differentiate the condition from appendicitis with perforation.

The finding of a diverticulum in a hernial sac is known as a Littre's hernia, and the occurrence may or may not be associated with the syndrome of intestinal obstruction. The relatively large number of cases reported lends a false impression of its frequency, and probably represents the desire of authors to report the bizarre rather than the more usual lesions. In 1943 Bird<sup>49</sup> collected 182 cases, of which 52 per cent were inguinal, 20 per cent femoral and 20 per cent umbilical.

Simple diverticulitis is actually more frequent than the literature suggests, its apparent rarity probably being due to its prosaic nature. Peritonitis following gangrene with perforation has occurred during intrauterine life. Stewart<sup>50</sup> states that the clinical picture is pathognomonic if there is localized tenderness on the right side just above McBurney's point at the level of the umbilicus. Wolfson and Clurman<sup>51</sup> attempt to differentiate appendicitis from diverticulitis by the severer and more colicky pain, greater distention and more pronounced vomiting accompanying the former. Despite these observations most clinicians are not so sanguine of their ability to differentiate the two conditions.

Foreign bodies found in these sacs include fish bones, gallstones, marbles and bullets.

Malignant tumors involving the diverticulum are rare, about 24 cases having been reported. Nygaard and Walters,<sup>9</sup> and Skinner and Walters<sup>10</sup> have collected 16 cases of sarcoma and 6 of carcinoma, to which group Albright and Sprague<sup>33</sup> have added another case of carcinoma. In 5 cases the tumors were clinically palpable before laparotomy. It is of interest that in 6 cases the lesions were demonstrated by barium studies of the small bowel.

In general, barium studies have been disappointing in demonstrating the sac. In 1943 Rousseau and Martin<sup>52</sup> reported a total of 13 cases in which diagnosis was made before operation. Tracey and Adams<sup>53</sup> and Carlson<sup>54</sup> have since reported individual cases. Albright and Sprague<sup>33</sup> advise the use of hourly films during the first five hours after ingestion of the barium meal to increase the radiologic accuracy of diagnosis.

### Treatment

The usual management at operation consists in excision with burial of the stump, as in appendectomy. Matt and Timpone,<sup>17</sup> however, strongly recommend resection of the contiguous ileum with primary anastomosis because of the known tendency of heterotopic tissue in the pouch to grow beyond the neck into the neighboring bowel. Perhaps a rational plan would be to use the simple and relatively safer appendiceal technic in the treatment of inflammatory lesions in which the frequency and importance of aberrant tissue is less, and to reserve

the ileal resection for cases with bleeding, in which heterotopic cells are certain to exist. Obviously, the patient's general condition, the size of the neck of the sac and other factors will influence this generalization.

The two following cases are reported because of their unusual complications, one of which is, to the best of my knowledge, recorded for the first time.

**CASE 1 (B91258)** C B, a 48-year-old Negress, was admitted to the hospital on July 26, 1944, with the complaint of intermittent swelling of the abdomen for 1 month, associated with moderate constipation and total absence of stool or flatus for 3 days. Nausea had been intermittent, but without vomiting. There had been no change in the color of the stools. Five months before admission, in another hospital, a diagnosis of congestive failure due to hypertension had been made, and the patient had been subjected to thoracenteses on the right side twice during her stay. After 2 months she had been discharged on maintenance doses of digitalis and had noted on occasions moderate dyspnea, orthopnea and ankle edema. A hysterectomy for a "fibroid tumor" had been performed at the age of 16.

Dyspnea and orthopnea were striking features, and the patient appeared moderately toxic. The head and neck revealed no significant abnormalities other than markedly engorged neck veins. The heart appeared slightly enlarged, and a harsh mitral systolic murmur was heard. There was impaired resonance over the right lower-lung field, with diminution of breath and voice sounds. Basal rales of the subcrepitant variety were heard on the left. The abdomen, which was quite distended and exquisitely tender throughout, demonstrated a fluid wave and shifting dullness. Peristalsis seemed hyperactive. A well healed lower midline incision was visible. Examination of the rectum, vagina and extremities was negative.

The rectal temperature was 98.9°F, the pulse 84 and regular, and the respirations 32 and labored. The blood pressure was 114/64 in both arms.

Examination of the blood disclosed a red-cell count of 2,630,000, with a hemoglobin of 40 per cent (Sahl), and a white-cell count of 10,600, with a normal differential. The urine was normal. A blood Kahn test was negative. The icteric index was 25, and the van den Bergh reaction indirect. The blood urea nitrogen was 11 mg and the total protein 5.4 gm per 100 cc, with an albumin of 2.6 gm and a globulin of 2.8 gm. The urine was positive for urobilinogen in a 1:10 dilution, the guaiac reaction of the stools varied from negative to ++++, but there was no gross blood. An electrocardiogram revealed strain of the left ventricle. X-ray films of the chest showed a thickened pleura at the right base and enlargement of the cardiac silhouette, with a hypertensive outline. Films of the abdomen disclosed fluid levels in the small bowel on repeated examinations.

The succeeding 20 days were marked by febrile rises to 101 to 102°F by rectum, bouts of distention relieved by insertion of a Miller-Abbott tube, episodes of clinical shock, diarrhea on occasions and absence of gross fecal blood. The usual therapeutic measures for cardiac failure were administered, and repeated transfusions of blood and plasma were given. On two occasions blood aspirated from the peritoneal cavity failed to clot on standing. On August 16 a laparotomy was performed under ethylene and ether anesthesia.

After celiotomy through a rectus incision approximately 3000 cc of blood was found in the peritoneal cavity. A diverticular mass, spherical in outline and 12 cm in diameter, was seen arising from the terminal ileum, about 45 cm from the ileocecal valve, it was firmly adherent to other loops of small bowel, the ascending and transverse colon and the right lateral and anterior abdominal walls. A slow ooze of dark blood was noted from a small hole in the base of the mass near its junction with the ileum. Resection of the diverticulum with a segment of the corresponding ileum, with primary anastomosis of the ileum, was performed.

The postoperative course was not remarkable, and the patient left the hospital in good condition on the 27th postoperative day.

Pathological examination revealed a 3 mm perforation in the base of the diverticulum and a communication with the ileum just large enough to admit a small probe, the entire mucosal lining was ulcerated and hemorrhagic, and the lumen was filled with liquid and clotted blood.

This case demonstrates a massive peptic ulcer in a Meckel's diverticulum, with perforation into the peritoneal cavity, hemoperitoneum and intestinal obstruction. This appears to be the first case with free bleeding into the abdominal cavity. Chaffin<sup>12</sup> reported a case with hemoperitoneum in which the blood was the result of a torn adhesion. There is a striking similarity between the case reported above and a case of gastric diverticulum associated with hemoperitoneum previously reported.<sup>16</sup>

CASE 2 (C17811) W. C., a 53 year-old man was admitted to the hospital on November 29, 1945, with a history of weakness and faintness of 2 weeks' duration following the passage of several "purple" stools whose color he interpreted as bloody. Two days later the color of the stools had returned to normal. The patient had been placed on a Sippy regime by a physician during this period. Two years prior to this episode he had experienced a similar attack and had been told that he had a peptic ulcer. He had received several transfusions at another hospital but had never had the clinical diagnosis confirmed by barium studies. He had never had pain at any time or bleeding from other areas of the body.

Physical examination revealed no abnormalities other than general pallor.

Examination of the blood disclosed a red-cell count of 2,170,000 with a hemoglobin of 51 per cent (Sahli) and a white-cell count of 4770, with a normal differential. The blood Kahn test was negative. The total protein was 5.5 gm per 100 cc. The bleeding, clotting and prothrombin times were normal, and the tourniquet test negative. Analysis revealed a low gastric acid. The stools were consistently negative for occult blood, ova and parasites. Repeated barium enemas and barium meals failed to demonstrate any lesion of the intestinal tract. There was no recurrence of bleeding at any time during the 7 weeks' stay. Repeated proctoscopic examinations failed to demonstrate any lesion of the rectum or sigmoid.

After repeated transfusions the patient was discharged in excellent condition and advised to return promptly if bleeding recurred. The diagnoses mentioned as most probable at time of discharge were Meckel's diverticulum and intestinal polyp but the failure of confirmation of melena during hospitalization was considered justification for conservative management.

The patient was readmitted on June 13, 1946. He stated that he had had a sudden and severe pain in the right lower quadrant beginning 3 days previously and that this pain had been constant in duration and quality, followed by vomiting on the day before admission. There had been no interval changes in stool color or habits.

On physical examination the patient did not appear acutely ill, the salient findings being confined to the abdomen which demonstrated marked tenderness in the area of McBurney's point, local rigidity, rebound tenderness, pain on coughing and absent peristaltic sounds.

The rectal temperature was 101.8°F, the pulse 80, and the respirations 20. The blood pressure was 104/64.

Examination of the blood disclosed a red-cell count of 4,500,000 with a hemoglobin of 84 per cent (Sahli) and a white-cell count of 15,000 with 79 per cent granulocytes.

A positive diagnosis of Meckel's diverticulitis was made, and an immediate laparotomy under spinal anesthesia was performed through a rectus incision. No free pus was encountered. An inflammatory diverticular mass communicating with two loops of the ileum was resected with involved sections of both loops of small bowel intestinal continuity being restored in each loop by end-to-end anastomoses. The convalescence was uncomplicated, and the patient was discharged in excellent condition on the 27th postoperative day.

Pathological examination of the specimen revealed a Meckel's diverticulum, which had established a fistula be-

tween itself and a higher loop of the ileum measured 11 by 8 by 5 cm and had undergone malignant degeneration with formation of a leiomyosarcoma. There were no evident metastases in the mesentery of the resected bowel nor had any metastases been noted at the time of laparotomy.

This case represents the seventeenth known case of sarcoma arising in a Meckel's diverticulum. It demonstrates the difficulty of diagnosis of this condition in adults and lends weight to the contention that cases of obscure intestinal bleeding should have laparotomies to establish the diagnosis when necessary.

## SUMMARY

The history, incidence, anatomy, pathology, complications and symptoms of Meckel's diverticulum are reviewed, and a plan of therapy for the complications is offered.

Two case reports illustrating rare complications are presented, one of which is the seventeenth case of sarcoma arising in a Meckel's diverticulum, and the other the first case reported in which a peptic ulcer that had developed within such a diverticulum had bled into the peritoneal cavity.

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## ELECTROENCEPHALOGRAMS IN NEUROPSYCHIATRIC DISORDERS AMONG SOLDIERS

### Results in 950 Cases

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IT WAS not until the latter months of 1943 and early 1944 that the Army made any extensive use of the electroencephalograph. By the middle of 1945 thirty-five brain-wave machines had been installed in different Army general hospitals throughout the United States. Six electroencephalographs were in use in overseas hospitals, and one overseas unit was completely mobile so that it could be taken to combat echelons for early study of cerebral injuries resulting from blast. The electroencephalograph adopted by the Army was the Grass machine of four or six channel type<sup>1</sup>.

Although the Army was late in developing adequate electroencephalographic departments, there is no doubt that important and interesting data have been accumulated and should enhance the knowledge, understanding and appreciation of the value or limitations of the brain waves. It is with the purpose of adding to the understanding and interpretation of electroencephalograms that the results of 1470 electroencephalograms on various neuropsychiatric disorders among 950 soldiers are briefly presented.

The material for this report was gathered and interpreted almost exclusively by me on patients at

the Cushing General Hospital from August 1, 1944, to January 1, 1946. The disorders studied included open and closed head injuries, almost all types of epilepsies or related conditions, brain tumors, headaches of undetermined origin, migraine, cerebrovascular accidents, psychoneuroses, psychoses and miscellaneous disorders, such as encephalitis, meningitis and trigeminal neuralgia. The patients with head injuries were subdivided into those having open, compound fractures of the skull without penetration of the dura or brain, those with open wounds with penetration of the dura and brain and those with closed injuries without open or penetrating brain injuries. Cases of cephalalgia comprised all patients with headaches of undetermined origin but none who gave a typical history of hemispheres or migraine, since these were tested as a separate group. The psychoneurotic group included a few cases of constitutional psychopathic personalities but no cases with a definite history of head injury of recent origin.

Head injuries were predominant in this series because a special head-injury section had been established in the neurologic and neurosurgical services of the hospital. The vast majority of these patients were received either from overseas via debarkation hospitals or from other Army hospitals

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in the Zone of the Interior from three to eight weeks after injury. A special study in selected cases of head injuries of the electroencephalographic findings, spinal-fluid analysis, post-traumatic seizures, neurologic and psychologic findings will be made available in a later paper.

All electroencephalograms were recorded from a four-channel Grass electroencephalograph. The brain waves were taken with the patient comfortably relaxed with eyes closed, on an easy chair in a properly shielded, grounded and darkened cage. Only strictly bed patients were examined lying down since artefacts frequently occurred if the subject was allowed to lie on the occipital electrodes, and the chances of obtaining sleep patterns in the records were greater in the reclining position. The standard type of lead-pellet electrode, with a small indentation for electrode paste, was used in all cases. In the method of applying electrodes, the time of recording from each area and the period of hyperventilation, the standards of operation set down by a War Department bulletin<sup>2</sup> was followed as closely as possible except that electrode placement had to be adapted to correspond to the cranial defect or area of injury and to compare this area as accurately as possible with the uninjured side.

Both monopolar and bipolar recordings were made except on the patients in whom localization was considered to be of no value. A specially designed rubber stamp of the position of all electrodes was placed on each record to determine accurately the point of greatest damage of intracranial lesions. Also, this diagram was found to be an excellent guide for placement of electrodes in subsequent electroencephalograms on the same patient. Odd numbers were used to designate left sided leads and even numbers for all right-sided leads. Most of the electrode placements and recordings were done by the same technician, who had been thoroughly and adequately trained at the School for Electroencephalographers of the Walter Reed General Hospital. Such consistency and uniformity in the placement of electrodes and methods of recording of brain waves is extremely important in the detection or elimination of artefacts and in comparing the tracings with previous records on the same patients.

The majority of the patients with open or penetrating wounds of the skull or brain had at least two electroencephalograms — one as soon as possible after admission to the hospital, and the other about two weeks after insertion of a skull plate or other operative procedure. A third or even fourth brain wave was frequently obtained just before the patient was discharged from the hospital. It was found that the presence of a tantalum plate in the skull (about 50 per cent of the open head injuries in this series) had no effect on the recording of electrical discharges from the brain. In patients with minor nonpenetrating brain injuries, psychoneuroses or

cephalalgias who showed normal tracings the electroencephalograms were not repeated, all borderline or abnormal records, however, were repeated if possible, and these records were carefully compared with previous ones. If typical Jacksonian seizures developed and the electroencephalograms repeatedly showed focal spike-wave discharges, the patient was presented to the neurosurgeon for possible cortical-scar resection.

Almost all the patients with head injuries who were found to have grossly dysrhythmic or focal records were placed on 0.032 gm of phenobarbital three times a day, and if convulsive seizures developed, this dosage was increased and perhaps Dilantin Sodium was also added. In this series of cases small or moderate doses of anticonvulsive drugs seemed to have no effect on the electroencephalograms and were not withheld before records were taken. This finding has also been confirmed in a recent survey.<sup>3</sup>

As indicated above practically all the electroencephalograms in this series were interpreted by me. This analysis consisted of an inspection of the entire record, the presence or absence of a dominant alpha frequency being noted. The amount and localization of any frequencies that were slower or faster than normal, the presence of paroxysmal discharges and the symmetry of the two hemispheres were carefully noted on the face sheet of each record. Any build-up after two or three minutes of hyperventilation was also noted. If any abnormality was seen, the tracing was studied in more detail and compared with previous electroencephalograms on the same patient. Sample cuts of any abnormal activity were taken from the record and mounted in folders that had been made for each case and contained, besides the sample brain wave, a clinical abstract of the patient, a copy of all operative procedures, psychologic data and photographs of any skull defects, intracranial foreign bodies and so forth.

Table 1 presents the results in the entire series. Of the 1470 electroencephalograms interpreted 32 per cent were normal, 16 per cent borderline, and 52 per cent abnormal. The results of the findings in the patients with head injuries are discussed below. The patients with epilepsy and related disorders included those in whom a history of some type of convulsive disorder was given, but this was not always proved by clinical observation. This fact probably explains the rather high incidence of normal or borderline records in this group. Of the 130 electroencephalograms showing definite cerebral dysrhythmia 77 were of the grand-mal pattern, 25 revealed petit-mal activity, 12 disclosed psychomotor seizures, 15 were probably best classified as demonstrating mixed types of seizure and 1 showed typical sleep spindles in a patient with narcolepsy.

A brain tumor was suspected in 23 patients, and 33 electroencephalographic tests were done on these subjects. Fifty-five per cent of the records were

definitely abnormal, and 37 per cent showed focal discharges, the underlying lesion being confirmed at operation in all cases. The 37 records of patients with headaches of unknown cause showed 68 per cent normal, 17 per cent borderline and 15 per cent abnormal. Migraine cases, however, yielded abnormal records in 33 per cent. The abnormality seen in the migraine tracings was, in most cases, generalized dysrhythmia, and this brings up again the interesting question whether migraine is related,

5 tested because of trigeminal neuralgia showed an abnormal record. The over-all incidence of abnormality in this group was 18 per cent. The abnormal records in the head-injury series were further classified as being generalized dysrhythmia if the record showed no focus of slow, fast or spike waves. Slow-wave foci were designated according to frequency as Grade I, or frequencies of 5 to 7.5 per second, Grade II, or 2 to 5 per second, and Grade III, or 0.5 to 2 per second. Foci of spike

TABLE 1 *Results of Electroencephalograms*

DIAGNOSIS	NO OF CASES	NO OF ELECTRO ENCEPHALOGRAMS	NORMAL TRACINGS		BORDERLINE TRACINGS		ABNORMAL TRACINGS	
			NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
Head injury	580	965	255	26	135	14	575	60
Epilepsy	190	280	94	33	56	20	130	47
Brain tumor	23	33	10	33	4	12	19	55
Cephalalgia	34	37	26	68	6	17	5	15
Migraine	24	28	11	39	8	28	9	33
Cerebrovascular accident	14	18	7	38	4	22	7	40
Psychoneurosis	41	48	39	81	6	13	3	6
Psychosis	20	28	19	70	4	14	5	16
Miscellaneous conditions	24	33	20	61	7	21	6	18
Totals	950	1470	481		230		759	
Averages				32		16		52

electroencephalographically at least, to the convulsive disorders. Cerebrovascular accidents included cases of thromboses or hemorrhages, few of these cases, however, were of recent origin, and this fact probably explains why not more than 40 per cent of the or fast waves were noted to be either continuous or paroxysmal. Table 2 presents the breakdown of the various types of head injuries according to this classification. From this analysis it will be noted that the slow-wave focus Grades II and III (frequencies of 0.5

TABLE 2 *Head Injuries according to Type and Electroencephalic Tracing*

TYPE OF HEAD INJURY	TOTAL NUMBER OF ELECTRO ENCEPHALOGRAMS	NORMAL TRACINGS		BORDERLINE TRACINGS		DYSRHYTHMIC TRACINGS		SLOW-WAVE FOCUS GRADE I		SLOW-WAVE FOCUS GRADE II		SLOW-WAVE FOCUS GRADE III		SPIKE-WAVE FOCUS	
		NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE
Open	141	34	24	20	14	29	20	13	9	25	18	4	3	16	12
Open penetrating	487	31	6	55	10	70	15	13	3	139	29	83	17	96	20
Closed	337	190	56	60	18	63	19	7	2	8	3	4	1	5	1
Totals	965	255		135		162		33		172		91		117	
Averages			29		14		18		4		17		7		11

electroencephalograms were abnormal. Only 6 per cent of the psychoneurotic records were abnormal, and since even so-called "normal subjects" show as many or even more abnormal patterns, it was believed that an abnormal electroencephalogram in this group was without much significance. On the other hand the 28 electroencephalograms of psychotic patients revealed an abnormality of 16 per cent, and 14 per cent were borderline. The miscellaneous group included 3 records of patients with a postmeningitic syndrome, which were abnormal, and 2 of patients following encephalitis, which were dysrhythmic. One case of the to 5 per second) occurred oftenest in the open, penetrating brain injuries — 29 and 17 per cent, respectively. Slow-wave focus Grade II was found in 18 per cent and Grade III in 3 per cent of cases with open nonpenetrating injuries. Only 3 per cent of patients with closed head injuries showed any slow activity. Generalized dysrhythmic records were seen in 20 per cent of open, nonpenetrating brain injuries and in 19 per cent of the closed head injuries. The spike-wave type of activity was present in 20 per cent of the penetrating brain wounds, 12 per cent of the open nonpenetrating injuries and in only 1 per cent of the closed head

traumas. After a lapse of three or four months, it was noted that the slow-wave focus frequently seen in open or penetrating brain injuries disappeared, and a spike-wave focus often became evident and undoubtedly indicated the development of cortical scars. Approximately 60 per cent of the patients showing spike-wave foci in the electroencephalograms developed convulsive seizures, and the presence of meningeal scars was confirmed at operation in several cases.

Clinical improvement and the lack of the so-called "post-traumatic syndrome" seemed to be more evident in the open or penetrating head injuries, although the electroencephalograms in these cases often remained grossly abnormal long after the patient had become better. This was in distinct contrast to the closed or minor head injuries, in which the electroencephalograms rapidly improved but the patient continued for many months to have headaches, dizzy spells, nervousness and so forth.

To determine the number of patients developing epilepsy after head injuries, a follow-up letter was given to each patient on discharge from the service. The patient was instructed to return these letters at the end of three months or immediately following any convulsive episode. This form letter requested the patient to describe any spells in detail, the date of the seizure and whether or not he was on medication at the time. Incomplete returns from these letters and from personal correspondence or subsequent observation of the patients indicate that to date about 24 per cent of patients with open, penetrating injuries of the brain in this series have developed post-traumatic epilepsy, in contrast to only about 5 per cent of those with closed or non-penetrating brain injuries. Since the electroencephalograms of about 60 per cent of patients with post-traumatic epilepsy demonstrated spike-wave or fast wave foci, it is quite suggestive that severe head injuries showing this type of electroencephalographic activity may sooner or later develop seizures and perhaps the early administration of anticonvulsive drugs may help to keep the patient free from seizures.

#### SUMMARY AND CONCLUSIONS

The results of 1470 electroencephalographic records in neuropsychiatric disorders among 950 soldiers are presented.

The head injuries made up the largest group tested (965 records) and included 141 electroencephalograms on open nonpenetrating injuries, 487 on brain wounds of the penetrating type and 337 on closed head injuries. The most frequent electroencephalographic abnormality in the open

nonpenetrating brain injury was generalized dysrhythmia and a slow-wave focus of 2 to 5 per second. A severe slow-wave focus of 0.5 to 5 per second was seen most frequently in penetrating brain wounds. A spike-wave focus was present in 12 per cent of nonpenetrating head injuries and 20 per cent of penetrating injuries. The tracings of about 60 per cent of patients developing post-traumatic seizures at one time or another showed spike-wave patterns.

Forty-seven per cent of patients with suspected epilepsy had abnormal records, the greatest majority being of the grand-mal type. No patients with post-traumatic epilepsy were included in this group.

Electroencephalograms on 24 different cases of migraine gave a definite abnormality in 33 per cent of subjects, whereas headaches of undetermined origin showed only 15 per cent.

Cases of cerebrovascular accident gave a fairly high percentage of abnormal activity (40 per cent). Brain tumors yielded 55 per cent abnormal activity, and of these abnormal records 37 per cent were definitely focal with the presence of the tumor confirmed by operation.

Patients with psychoneuroses showed only 6 per cent abnormal records. The frank psychoses, however, gave 16 per cent abnormal tracings, suggesting that the psychoses have some effect on brain waves — mainly a disturbance in the basic alpha rhythm.

Of the miscellaneous disorders tested, postmeningitic and postencephalitic syndromes showed the greatest number of abnormalities in the electroencephalograms.

The electroencephalogram is of definite value in localizing the greatest point of damage in brain injuries by the presence of a severe slow-wave focus. After three or four months this focus is frequently replaced by a spike-wave focus.

The electroencephalogram is also considered to be of definite aid in the diagnosis of various types of epilepsies and related disorders. It is useful in localizing brain tumors, provided the tumors are near the surface of the cortex and are not accompanied by increased intracranial pressure. Several cases of migraine showed abnormal records, suggesting that this malady is, at least electroencephalographically, related to the epileptic disorders. In all other neuropsychiatric disorders tested, the electroencephalograms were of doubtful or negative value.

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## MEDICAL PROGRESS

### ENDOSCOPY (Concluded)\*

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#### GASTROSCOPY

##### *Instruments*

Six years ago Kenamore described a biopsy forceps for the flexible gastroscope. In a study of gastric lesions by means of biopsy specimens removed endoscopically, Kenamore, Scheff and Womack<sup>46</sup> presented 4 cases illustrating the value of the instrument as a positive method of differentiating benign and malignant gastric lesions. The instrument, which in trained hands is regarded as safe and as offering a method of more exact study of gastric diseases, is a flexible steel cable of fine caliber that can be attached externally to the gastroscope, whose diameter is thereby increased by only 3 mm. There is much to be gained by a suitable gastroscopic biopsy forceps, but I should much prefer to have such a forceps incorporated into the instrument, thus eliminating any external attachments that might interfere with smooth passage.

Hufford<sup>47</sup> has described a new light-weight flexible gastroscope known as the Eder flexible gastroscope, whose principal advantages are claimed to be reduced diameter of the flexible section by approximately 3 mm, greater flexibility, reduced weight and a superior optical system, with better magnification. Hufford considers this flexible gastroscope easier to handle and to manipulate, with less discomfort and tension on the part of the patient.

##### *Technic*

Robinson<sup>48</sup> believes that fluorescein aids in outlining and demonstrating a gastric ulcer and thus makes possible a more accurate estimate of diameter of the ulceration at the time of gastroscopy. Ten cubic centimeters of fluorescein is introduced into the stomach through an Ewald tube after the gastric contents have been drained. Gastroscopy is carried out in the usual manner.

##### *Complications*

Paul and Antes<sup>49</sup> reported a perforation of the esophagus by the flexible gastroscope resulting in retropharyngeal abscess formation. Prompt recognition and treatment effected a cure. The complication has become rare since the introduction of the flexible gastroscope.

Berk<sup>50</sup> observed a case of pneumoperitoneum following gastroscopy without evidence of perforation at laparotomy fourteen hours later. Gastroscopy was accomplished without difficulty, and mucosal details could be seen after inflation. The striking feature of the examination, however, was the fact that the stomach could not be kept inflated. After removal of the gastroscope, the patient complained of a sense of fullness and tightness, and physical examination showed signs of pneumoperitoneum. At operation there was no fluid collection and no evidence of inflammation or peritonitis on the serosal surface of any of the viscera. Thorough examination of the stomach and the abdominal portion of the esophagus failed to disclose any tear or perforation. The abdomen was closed tightly without drainage. Convalescence was uneventful.

##### *Gastroscopic Studies*

Howard<sup>51</sup> asks the question, "What is the real value of gastroscopy?" According to him, gastroscopy enables one to see clearly a large part of the interior of the stomach, to visualize most gastric tumors and some gastric ulcers and to diagnose gastritis more properly. The gastroscope is a useful adjunct to the x-ray apparatus but does not supplant it. The diagnosis of chronic gastritis is the unchallenged field of gastroscopy, for the condition of the stomach's mucosa can be determined much better by direct inspection than by inferences from the study of its secretions or from the rugal pattern on the roentgenograms. Frequently, the height of the rugae is controlled by the tone of the muscularis mucosae, and elevated folds seen on the skiagrams can be ironed out by the inflation of the stomach with air. With the gastroscope reddening of the mucosa, edema, ulcerations resembling canker sores and a granular mucosa may be observed, sometimes, nodules are seen on the folds, or there may be atrophy of the gastric mucosa with striking thinning and a blue-gray color.

##### *Dyspepsia and Gastroscopy in the Armed Forces*

Before Pearl Harbor, Tavares<sup>52</sup> examined by gastroscopy 100 consecutive military patients. He believes that as a diagnostic procedure gastroscopy deserves the place in military medicine, in peacetime or in war, that it merits in civil practice. The outstanding indication for gastroscopy was the group of conditions consisting of the dyspepsias.

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present in 72 per cent of patients. A normal stomach was found in 20 per cent of cases examined. By far the largest group under the general classification of gastritis consisted of 25 patients with superficial gastritis.

Halsted et al.<sup>42</sup> correlated gastroscopic and psychiatric studies of soldiers with chronic or non-ulcerative dyspepsia. Their study included 110 combat soldiers in a field hospital in the Fifth Army area in Italy during a seven-week period of static warfare. Clinical, roentgenographic, psychiatric and gastroscopic observations were made. The gastric mucosa was normal in 59 per cent of cases, and mild to moderate abnormalities consisting of redness, edema and exudation were observed in 41 per cent. There was no correlation between the appearance of the mucosa and the symptomatology, the symptoms being the same whether or not the mucosa was normal. Eighty-four and a half per cent of the total and 75 per cent of patients with gastroscopic abnormalities had a psychoneurosis, 15.5 per cent were psychiatrically normal. The clinical study is suggestive that the gastroscopic abnormalities noted — being those of superficial gastritis — represented functional circulatory changes resulting from nervous tension rather than the signs of organic disease.

Schwartz and Perlmutter<sup>43</sup> made a gastroscopic, roentgenologic and psychiatric study of chronic dyspepsia in the Mediterranean Theater. Gastroscopy was important as the only accurate method available for ruling out or confirming the diagnosis of chronic gastritis. Seventy per cent of subjects examined showed definite psychoneurosis. Chronic gastritis was the admitting diagnosis in 11 cases, but in only 4 was this confirmed by gastroscopic examination.

Chamberlin,<sup>44</sup> in a brief comment on gastroscopy in a report on military gastroenterology, states that "gastroscopy was a useful augmentation to the armamentarium of the gastroenterologist at war, but would have been more so had there been more gastroscopes and more gastroscopists."

#### *Acute Gastroenteritis*

Schwartz<sup>45</sup> examined by gastroscopy 20 patients who had recovered from a severe acute gastroenteritis as a result of food poisoning. Gastroscopy was performed three or four weeks after the onset of symptoms. He concluded that there was a lack of correlation between the gastroscopic findings and the symptoms in the majority of patients examined.

#### *Atrophic Gastritis*

Ortmayer, Balkin and Humphreys<sup>47</sup> report a case of chronic erosive granulomatous atrophic gastritis in which x-ray examination showed a constant narrowing in the prepyloric region with absent peristalsis and apparent shortening of the antral lesser curvature. Gastroscopy also gave the impression

of a narrowed antrum. A yellowish-white area extended from the lesser curvature of the antrum across the anterior margin of the angulus and 4 cm higher along the lesser curvature of the body of the stomach. This area was certainly an extensive erosion. Its proximal margins were reddened. The musculus sphincter antri looked infiltrated and stiff. In the higher stomach blood vessels were visible. The clinical diagnosis was carcinoma of the antrum and lesser curvature, with atrophic gastritis. At operation a rather soft lesion was palpated on the lesser curvature. The resected specimen showed a 4-by-5-cm., shallow, irregular ulceration that was barely perceptible. The pathological diagnosis was subacute to chronic granulomatous ulcerative gastritis, with no clue to its etiology. The authors believe that this interesting lesion has not previously been described.

#### *Chronic Gastritis*

In a study of chronic gastritis, Maimon and Palmer<sup>48</sup> state that the interpretation of the gastroscopic findings is not always easy, since variations in the appearance of the gastric mucosa noted with repeated examinations of the same stomach are extremely frequent. The frequent transition from one to the other suggests that the two may be variants of the same process. In a case reported no correlation between the gastroscopic findings and the clinical course of the patient could be noted. In another case seven gastroscopies for gastric ulcer were performed during a four-year period. The first revealed severe atrophic gastritis of the upper half of the stomach associated with areas of hemorrhage, confirmed by four succeeding examinations in the following years. Subtotal gastrectomy was carried out because the ulcer continued to recur. Histologic examination disclosed, in addition to a benign gastric ulcer, diffuse atrophic hemorrhagic gastritis and metaplasia to an intestinal type of lymph node. Gastroscopic examination of the remaining stomach three years later disclosed a normal mucosa. Even with severe changes, including metaplasia, atrophic mucosa may return to normal or at least form a normal-appearing surface. In general, however, the observations indicate that severe and widespread atrophy tends to continue unchanged. Furthermore, the return of the mucosa to a gastroscopically normal appearance does not prove the presence of a normal mucosa, for, as in pernicious anemia during a therapeutic remission, the apparently normal mucosa is unable to secrete acid gastric juice. There seems to be considerable evidence of an etiologic rather than an accidental relation between pernicious anemia and tumors of the stomach. The conclusions of Maimon and Palmer are as follows:

Chronic gastritis as diagnosed gastroscopically toward a persistent or recurrent course with predictable variations in type, severity and



the stomach. Repeated examinations of two patients with quite consistently normal findings suggest the tendency of the normal stomach to remain normal. On the other hand, phases of normality were not infrequently found in stomachs usually exhibiting a chronic gastritis of one kind or another. Repeated examinations in individual patients over periods varying from two to eleven years suggest that superficial and hypertrophic gastritis may be variations of the same process rather than separate and distinct entities. The prognostic implications of both the moderate and severe grades of superficial and hypertrophic gastritis are not significantly different, both tending to prolonged chronicity. Atrophic changes without an admixture of the superficial or hypertrophic types were observed to be constant for periods up to five years, on the other hand, in some cases atrophic gastritis did seem to appear as a sequela of hypertrophic and superficial gastritis. Atrophic gastritis, when severe, tends to persist, but return to normal has been observed. Atrophic changes are more frequent in the upper third of the stomach whereas superficial and hypertrophic changes occur more often in the middle portion. Gastritis of various types has been observed gastroscopically in many examinations in 14 patients over periods up to eleven years in duration without detectable serious consequence. In these 14 patients it has not been possible to correlate the appearance of the gastric mucosa with symptoms of any kind. While mucosal changes were observed in 6 patients subjected to x-ray therapy the type of change was not constant or consistent and could not be correlated with the appearance of the mucosa prior to roentgen irradiation or with therapy itself. Two patients with both superficial and hypertrophic gastritis prior to supradiaphragmatic bilateral vagotomy were found to have only superficial changes after the operation. Regardless of attractive theoretical considerations the clinical significance of chronic gastritis remains unproved.

### *Edematous Gastritis*

Loeper<sup>59</sup> believes that the condition that he calls "edematous gastritis" is caused by the ingestion of certain foods, particularly mollusks, crustacea, fish and sausage. It often alternates with urticaria, of which it seems to be an internal manifestation. Gastroscopy assists in the diagnosis. An edematous swelling of the mucosa, with a pale central zone and a darker periphery, may be present. The duration of the edematous gastritis may be from two to eight days. Treatment consists of a strict diet and administration of bismuth and charcoal. Desensitization may be effected by the administration of peptone and pepsin prior to meals.

### *Postoperative Gastritis*

According to Christiansen,<sup>60</sup> postoperative gastritis is characterized by polymorphism. There are superficial, hypertrophic, erosive, atrophic or ulcerous elements. The condition develops independently of the presence of free hydrochloric acid or of the ability of the stoma to attain rhythmic contraction. If objective improvement occurs, it affects only the erosive and ulcerative elements, the atrophic and hypertrophic changes appear irreversible. Effective therapy is not known. The most helpful treatment is perhaps a combination of ulcer diet and gastric lavage, but subjective improvement is not always accompanied by objective improvement, and in spite of amelioration the gastritis may progress. Postoperative gastritis must be considered one of the gravest disorders of the stomach.

### *Gastric Ulcers*

Ricketts and Pollard<sup>61</sup> analyzed 1297 patients, who were studied both by x-ray examination and by gastroscopy. In 172 cases in which both examinations were negative no satisfactory clinical diagnosis was made in 60, in 112 cases the clinical diagnoses comprised a wide variety of extragastric disorders and diseases. In the 355 cases with conflicting gastroscopic and roentgenologic findings gastroscopy failed to reveal lesions visible on x-ray study in 46 cases, including 22 of benign ulcer, 21 of carcinoma (11 proved at operation or necropsy), 2 of benign polyposis and 1 of gastric diverticulum. Conversely, positive gastroscopic and negative roentgenologic findings were obtained in 309 cases, including 269 of chronic gastritis, 26 of benign ulcer, 10 of carcinoma (the diagnosis being proved at operation or autopsy in 5 cases) and 4 of benign polyp, 1 with malignant degeneration. Three cases with a gastroscopic and roentgenologic diagnosis of carcinoma proved on histologic examination to be tumor-like gastritis. In the complete clinical study of gastric disease, gastroscopy and x-ray study are invaluable, although not infallible, procedures.

Pollard, Bachrach and Block<sup>62</sup> believe that with further advances in diagnostic technic, particularly regarding gastroscopic visualization, it may become possible to determine more accurately from the size and appearance of an ulcer whether it is likely to heal under adequate medical management, and how soon healing can be expected.

Brick<sup>63</sup> has written a preliminary report on irradiation effects on the stomach with a 1,000,000-volt machine. A case of ulceration of the stomach with perforation and hemorrhage as a result of irradiation successfully treated surgically has been reported, as well as a case of gastroscopic confirmation of an ulcer noted by x-ray examination. The importance of these observations lies in obtaining accurate knowledge about the tolerance of various human tissues in this age of supravoltage and atomic energy.

### *Carcinoma*

Rickles<sup>64</sup> reports a case in which five primary cancerous lesions of the stomach were present and were treated by transthoracic gastrectomy. Pathological study of the specimen showed an ulcerating carcinoma of the cardiac end of the stomach and four papillary adenomas of the gastric mucosa apparently arising from adenomatous polyp. These tumors were separated by normal mucosa and submucosa.

Maimon and Palmer,<sup>65</sup> in a review of the incidence and diagnostic procedures in gastric carcinoma, state that the value of prolonged and repeated gastroscopic examinations cannot be too strongly stressed, since parts of the stomach not clearly visualized at one examination were frequently seen at the time of another examination.

several days or weeks later. The change in the appearance of a lesion was often so marked in a few days that the examiner was able to make a correct diagnosis even though this had not been possible at the time of the initial examination. Differences in peristaltic action, spasm and the superficial appearances of a lesion may well account for the changing picture. Although gastroscopy is a valuable adjunct in the diagnosis of gastric carcinoma the criteria for determining the resectability of a lesion by this method need further study. The correct diagnosis was made in 84.6 per cent of 163 patients so examined. In 15.4 per cent the examination was inconclusive owing to the technical difficulties preventing satisfactory passage of the instrument or failure to visualize the lesion, or the diagnosis was incorrect because of inability to differentiate neoplasm from ulcer, hypertrophic gastritis, lymphoma and sarcoma.

Schindler<sup>65</sup> has discussed the relative surgical curability of certain gross types of gastric carcinoma. He believes that microscopical grading is not too reliable and that perhaps a better method would be to base the prognosis and the therapeutic procedure on gross types of carcinoma. The Borrmann classification has been used in which Type I is the sharply limited polypoid tumor, accounting for 2.9 per cent of all gastric carcinomas. Type II, which is also a sharply limited tumor, consisting of an ulcer surrounded by an elevated wall sharply demarcated all around, occurs in 17.6 per cent. Type III, which occurs in 16.3 per cent, is also sharply limited, consisting of an ulcer surrounded by an elevated wall, but the wall does not surround the whole circumference of the ulcer, the ulcer blending diffusely at some point with the neighboring mucosa. Type IV comprises the diffusely infiltrative tumors (63.2 per cent). There is some evidence that Types I and II are relatively more curable than Types III and IV. By a combination of x-ray study and gastroscopy the gross type of a gastric carcinoma can usually be identified reliably before operation.

Moernach and Kirklín<sup>67</sup> compared gastroscopy and roentgenology in 100 selected cases of proved carcinoma of the stomach. The diagnosis by gastroscopy was correct in 70 cases, indeterminate in 10 and incorrect in 20, and that by x-ray examination was correct in 52 cases, indeterminate in 6 and incorrect in 42. The source of greatest error in gastroscopic diagnosis of carcinoma of the stomach was in the differentiation of this lesion and severe hypertrophic gastritis. It is pointed out that repeated roentgenologic examination of the stomach is sometimes required before a definite opinion regarding the presence or absence of a gastric lesion can be expressed and, if one is present, its character determined. In contrast, it is too frequently assumed that a definite opinion should be expressed as a result of a single gastroscopic examination. That repeated gastroscopic examinations are often as essen-

tial as repeated roentgenographic examination in arrival at a correct diagnosis is well illustrated by the data presented. The authors conclude that roentgenology is preferable to gastroscopy as a routine procedure in the diagnosis of carcinoma of the stomach, because of its ease of performance, rapidity, greater safety and the fact that there are fewer contraindications to its use than to that of other methods. Gastroscopy is of extreme value as an adjunct to roentgenology and clinical diagnosis in the study and diagnosis of carcinoma of the stomach. This is especially true in cases in which the roentgenologic findings are indefinite and in those in which the roentgenologic and clinical observations are at variance. The close collaboration of the gastroenterologist, roentgenologist and gastroscopist is of great importance in improving the chances of earlier diagnosis of carcinoma of the stomach.

Stout<sup>68</sup> studied 150 resected stomachs and found atrophic changes in 50 per cent of cases with duodenal ulcer, 60 per cent with gastric ulcer and 94 per cent with gastric carcinoma. It is apparent that atrophic changes and cyst formation accompany carcinoma of the stomach, but to detect a causal relation, one must find cancer epithelium and gradations between altered cells. Such a relation has not been proved.

#### *Leiomyosarcoma*

Schindler and his associates<sup>69</sup> discussed the roentgenologic and gastroscopic diagnosis of leiomyosarcoma of the stomach and its possible relation to pernicious anemia. In the 4 cases considered the diagnosis of a gastric tumor was missed at one x-ray examination in 1 case and at two in another. In these cases the presence of a gastric tumor was found at gastroscopy. In both cases the tumor could be demonstrated at a repeat x-ray examination when the proper technic was used. These cases prove the fact that the method of filling the stomach completely with barium suspension and then taking films is unsatisfactory. The barium must be replaced routinely by the relief method. The diagnosis of benign submucosal tumor at x-ray examination can be hazarded if a sharply defined round filling defect with a central niche is noted. The authors state that in none of 4 cases was the correct diagnosis made at gastroscopy but that in 2 features were described in the gastroscopic protocol that had a certain relation to submucosal tumors and this relation had been stated. The important gastroscopic finding is that of a soft, protruding mass with hemispherical protrusion sloping gently toward the gastric wall. The authors conclude that in 3 cases the x-ray diagnosis would not have been impossible and that in 3 cases the correct gastroscopic diagnosis should have been made. In 1 case there was the possibility of pernicious anemia leading to the formation of leiomyosarcoma.

### *Isolated Hodgkin's Disease*

Browne and McHardy<sup>70</sup> reported 2 cases of isolated Hodgkin's disease of the stomach in the first of which gastroscopy revealed in the proximal two thirds of the stomach a widespread polypoid hyperplasia with nodulations and ulceration, covered in part by a grayish exudate, seemingly held rigid, but remarkably distensible and with an uninvolved pyloric segment. In the second case gastroscopy was not done. The authors believe that a clinical diagnosis cannot practicably be made with present knowledge of the disease, but that in its simulation to neoplastic disease it often manifests itself sufficiently early and significantly to indicate resection.

### *Hemorrhage from Gastritis*

Jones<sup>71</sup> emphasizes the fact that gastritis alone is occasionally the source of an exsanguinating loss of blood. In the absence of definite roentgenologic findings, or when supplemental evidence regarding the nature of the bleeding lesion is desirable, endoscopic examination should be performed as soon after major bleeding has ceased as it can safely be done. Gastroscopy, in experienced hands, is the only way to demonstrate an active gastritis that is responsible for upper-segment hemorrhage.

Schatzki<sup>72</sup> also believes that gastritis may cause marked hemorrhage, particularly if many erosions are present. The roentgenologic diagnosis of gastritis is difficult and is possible in only a small number of cases. The erosive form, in which bleeding is most frequent, is rarely demonstrable, but if it is, the characteristic appearance is one of multiple shallow craters surrounded by a halo of edema. In acute alcoholic gastritis, which often causes hemorrhage, evidence of marked hypersecretion, with some swelling of the folds, is seen. At times this swelling produces a tumor-like appearance, but it usually disappears within a few days. On the other hand, in gastritis, the stomach may appear completely normal roentgenologically, and only by gastroscopy may the diagnosis be made.

### *Hereditary Hemorrhagic Telangiectasis*

Kushlan<sup>73</sup> has reported a typical case of hereditary hemorrhagic telangiectasis with chronic gastrointestinal bleeding of fifteen years' duration. Gastroscopy offers an invaluable aid in determining the presence of the characteristic lesions in the stomach, since x-ray examination of the gastrointestinal tract appears to be of no value in these cases. Rutin therapy may represent the long sought for specific remedy for hereditary hemorrhagic telangiectasis.

### *Salicylism*

Caravati<sup>74</sup> performed gastroscopy on 20 patients during salicylism. The stomach was satisfactorily visualized in each case but no abnormality of consequence was observed except in a case that showed

moderate increase of highlights with erosions of the gastric mucosa visualized at Depth two. This was thought to represent probable localized minimal superficial gastritis.

### *Gastroscopy in Acute and Chronic Hepatitis*

Bank and Dixon<sup>75</sup> made gastroscopic observations in 43 cases of acute and chronic hepatitis. In no case did gastric symptoms exist prior to the onset of hepatitis. X-ray examinations of the stomach, duodenum and gall bladder were negative in all. Gastroscopy did not reveal significant evidence of gastritis. The minimal findings observed in some patients were not considered contributory to the patient's gastrointestinal symptoms.

### *Gastric Varices*

Although esophageal disease is usually a contraindication to gastroscopy, Moersch<sup>76</sup> believes that gastroscopy should be considered in cases of esophageal varices in which injection of the varices with a sclerosing solution is contemplated. Inspection of the stomach is advisable to determine whether or not varices are present in the stomach. In the experience of Moersch, injection of esophageal varices will be disappointing if varices are also present in the stomach. Although gastric varices can be identified in a high percentage of cases on roentgenologic examination, gastroscopy has been found more accurate in this respect than roentgenologic methods. So far, Moersch has encountered no difficulty as a result of gastroscopy in the presence of esophageal varices, but it is not advisable to carry it out during an active phase of bleeding.

## PERITONEOSCOPY

### *Needle Biopsy of Liver*

Peritoneoscopy is so frequently performed to obtain a biopsy of the liver that it seems only fair to mention the alternative method of needle biopsy. This can apparently be done safely in most cases of diffuse liver disease but is done blindly and will not be likely to pick up isolated areas of metastatic carcinoma.

Davis, Scott and Lund,<sup>77</sup> have performed needle biopsy of the liver on 68 patients since 1939. They have found the procedure most useful in the diagnosis of carcinoma of the liver and in establishing the nature of a diffuse parenchymal disease, including cirrhosis. There were no fatal cases.

Van Beek and Haex<sup>78</sup> have obtained valuable information from aspiration biopsy of the liver in a case of infectious mononucleosis and in 4 cases of sarcoidosis.

### *Cirrhosis of the Liver*

The treatment of cirrhosis of the liver is beyond the scope of this report, but it is of interest that the result of treatment at varying intervals of time can

be advantageously studied by needle biopsy of the liver or by biopsy obtained at the time of peritoneoscopy.

Recent advances in the therapy of cirrhosis have been discussed by Morrison<sup>79</sup> in a series of 62 patients studied from 1938 to 1945. These patients were divided into three groups according to the method of treatment most advisable at the time. The best results were obtained in the third group of 20 patients, who were treated intensively with a combined therapy consisting of a maximum protein, high-carbohydrate, low-fat diet, daily injections of 5 cc of a whole-liver extract, highly potent injections of components of the vitamin B complex, daily components of the vitamin B complex orally and multiple vitamin capsules orally, together with 2 gm each of methionine and choline daily. The intensive combined method of therapy resulted in a remission of all signs and symptoms in 64 per cent of cases in the group without ascites, as compared with remissions in only 10 per cent of cases in the control group, in the group with ascites remission occurred in 34 per cent of cases, as compared with none in the corresponding control group.

Lowry, Ashburn and Sebrell<sup>80</sup> maintained rats on a cirrhosis-producing diet for sixty-three to eighty-four days, and the status of the liver of each rat was determined at that time by biopsy. The rats were then treated by the daily administration of large amounts of choline chloride or by the use of a diet containing large amounts of casein. The gross and microscopical appearance of the liver after treatment was compared with the biopsy findings. During the period of treatment a striking improvement in the gross and microscopical appearance of the liver occurred. Although therapy did not have a recognizable effect on the fibrous tissue present, it apparently prevented further progression of the cirrhotic process and produced improvement in the microscopical appearance of the parenchyma.

### Value of Peritoneoscopy

Miqueo Narancio et al<sup>81</sup> have used the peritoneoscope chiefly in the attempted determination of inoperability, in borderline cases when clinical evidence of such inoperability does not exist. They have evaluated the procedure from the following three standpoints: the possibility of avoidance of an unnecessary celiotomy, the rate of operative mortality and morbidity of exploratory celiotomy vs peritoneoscopy, and the economic factor. In their series peritoneoscopy disclosed the disease to be so extensive that exploratory celiotomy was avoided in 39 cases, or 48.8 per cent. The average duration of hospitalization of these patients was forty-eight hours. The single death that occurred in the group of 80 patients was the result of intraperitoneal hemorrhage in a patient with cirrhosis of the liver and a low prothrombin level. No obvious source of bleeding could be found on post-mortem examination.

This record may be contrasted with that for exploratory celiotomy for cancer which is generally in the neighborhood of 8 per cent. The brief period of hospitalization is of economic significance to the patients. At present the total minimum cost to a patient occupying an inexpensive private room for two weeks is \$195 with anesthesia and operating-room charges, compared to a cost of \$58 for peritoneoscopy.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 33301

#### PRESENTATION OF CASE

A seventy-three-year-old woman entered the hospital because of swelling of the right leg

She had been well until five weeks before entry, when, just after going to bed, she suddenly had a chilly sensation and began to feel feverish. At the same time she developed a severe productive cough, yielding about a cupful of clear, liquid sputum a day. Her strength gradually ebbed until she could no longer leave her bed. She subsisted on milk and soups. Two days before entry the district nurse, who stopped daily to bathe the patient, noticed that the right leg was swollen. The patient herself had observed only that the leg was "heavy." It had not been painful, cold or numb.

Twenty-nine years before entry the patient had had epidemic influenza complicated by slight swelling of the right leg and pain deep in the calf. She was told that she had phlebitis and myocarditis. For about twenty years she had had mild "bronchitis." Four years before entry she began to have difficulty in climbing the two flights of stairs to her apartment because of exhaustion and some dyspnea. She slept on two pillows. She denied ever having experienced chest pain or palpitation. The weight had been over 250 pounds for many years. She did not believe that she had lost much weight during the present illness.

Physical examination revealed an extremely obese woman lying flat in bed without distress. The skin was thick and dry. The eyebrows were thick, but there was no axillary hair and the pubic hair was sparse. There were a few rales at the left base. The heart sounds were faint and irregular, with what were apparently frequent extrasystoles. The abdomen was normal, except for the extreme obesity. Brawny swelling of the right leg up to the groin was noted, and there was pitting edema over the foot which was cyanotic and slightly cooler than the left. Dorsalis pedis and posterior tibial pulses were palpable and equal on

100°F, the pulse 70, and blood pressure was 140

Examination of the blood showed a hemoglobin of 12.2 gm and a white-cell count of 18,350, with 86 per cent neutrophils. The urine was normal, except for a + test for albumin. A stool was brown and formed and gave a negative guaiac test.

An x-ray film of the chest disclosed a wedge-shaped area of increased density, extending upward and forward from the left lung root in the upper lobe to the anterior chest wall. The cardiothoracic ratio was 15/27. An electrocardiogram showed auricular fibrillation and a ventricular rate of 70. The voltage and axis were normal. There were sagging ST segments in Leads 2 and 3, slightly low and upright T waves in Leads 1, 2 and 3, a small R wave and a flat T wave in Lead CF<sub>2</sub>, a slightly sagging ST segment in Lead CF<sub>4</sub> and upright T waves in Leads CF<sub>4</sub> and CF<sub>6</sub>.

The patient was placed on bed rest and a low-salt, reducing diet. A second x-ray film of the chest on the tenth hospital day showed no change. On the eleventh hospital day the patient was cyanotic and moaning in short gasps. The blood pressure was not obtainable. After fifteen minutes the heart beat and respirations ceased.

#### DIFFERENTIAL DIAGNOSIS

DR RICHARD J CLARK: May we see the x-ray films? This, I assume, is the band of density described.

DR TOUFIC H KALIL: Yes, it was described as going diagonally upward.

DR CLARK: I judge that the heart was displaced to the right—at least there seems to be considerable prominence on the right side. This band of density in the lateral view does not show up particularly well in the anteroposterior view.

DR KALIL: For that reason I think that it is probably not a band of atelectasis. There is no reason to suspect that atelectasis was present in the upper lobes.

In this lateral view the anterior margin of the trachea is displaced posteriorly.

DR CLARK: What about the hilar shadow?

DR KALIL: That is an unusual shadow. The pulmonary trunk is markedly enlarged, and the comma-shaped shadows on each side are markedly enlarged. Right and left pulmonary arteries. The left main bronchus is displaced downward. Usually, that means a collapsed lower lobe. In this case it is pressure from the large left pulmonary artery above. There is no increase in markings on the left, but there is some in the right lower lobe, representing atelectasis.

DR CLARK: Would you care to say whether that shadow, from the x-ray point of view, is consistent with a pneumonic process?

DR KALIL: No, it is not.

DR CLARK: I think that this is an example of a case in which the impression of the x-ray picture from the description in the record is quite different.

from that produced by the actual films. I am taken aback by the appearance of the x-ray films.

This case involves problems regarding the leg, the lungs, the heart and finally the mode of exitus. Although there may be interrelations, I shall take the points up separately.

Twenty-nine years prior to entry the patient had an episode consistent with acute phlebitis in the right leg. We are told nothing of any interim difficulty. Two days before admission, edema of the right leg was again noted, but apparently with little other symptomatology than a "heavy" sensation. This appeared after about five weeks of bed invalidism. Cases of unilateral leg edema first bring to mind a local circulatory disturbance. The leg was slightly cyanotic and cool, but showed palpable arterial pulses. Nothing is said regarding tenderness. The possibility of a pelvic mass that produced unilateral venous stasis must be considered, but we are told nothing regarding rectal or pelvic examination, and there is no way in which I can arrive at any such diagnosis. I am left with the conclusion that a recurrent phlebitis of the leg must have developed.

Next comes the problem of the lung lesion. Five weeks before admission there was a sudden onset of chilly sensations and feverishness associated with a severe productive cough and the raising of clear, liquid sputum. The presence or absence of blood is not mentioned. Apparently, there was no chest pain. This process was accompanied by progressive loss of strength. On entry the lungs showed only a few rales at the left base, but on x-ray examination there was the wedge-shaped lesion that we have seen. We may reasonably assume that the x-ray findings were associated with the sudden onset of the illness five weeks previously. The possibilities to consider are, first, cancer, second, tuberculosis, third, pulmonary infarction and, finally, an acute pneumonic process. The polymorphonuclear leukocytosis on entry was most probably associated with the leg lesion and cannot influence strongly the diagnosis of the lung lesion. In spite of the history of bronchitis for twenty years, I consider the onset too abrupt to have been associated with primary cancer of the lung, nor does the x-ray description especially suggest this. For practically the same reason, I shall dismiss tuberculosis. A pneumonic infection of the virus type could give the entire lung picture and not infrequently drags out over a period of several weeks, with continuation of x-ray changes. With such an infection there may well be associated atelectasis. The acute process may also have resulted from pulmonary infarction. The onset is by no means typical of the classic description of pulmonary embolism, but we have learned increasingly in recent years that vague symptoms of pneumonia, especially in patients with cardiovascular disease, often represent infarction of the lung. It is possible that this patient had one of

the insidious, slowly progressive types of phlebitis at the onset, which manifested itself only in producing an embolus but which subsequently progressed to the point of venous obstruction. On the other hand, the location of the lesion in the left upper lobe is definitely against pulmonary infarction, and the progressive weakness fits better with a low-grade pneumonic infection. Also, it would be most unusual for an infarct of the lung to be so definitely wedge shaped and to show no change five and six weeks after onset. Pulmonary infarction does not usually induce the coughing up of a cupful of clear sputum daily. Although this consideration of pulmonary infarction intrigues me, I shall pass it by in favor of a pneumonic process, probably associated with some atelectasis.

Now we come to the question of the heart. For four years the patient had had exhaustion and dyspnea and had required two pillows to sleep comfortably. She was said to have had myocarditis, which means little, twenty-nine years previously. The heart sounds were distant and irregular, but no murmurs were described. On x-ray study the heart was enlarged, the borders extending 2 cm beyond the average cardiothoracic ratio. Its shape was somewhat unusual, suggesting prominence in the region of the pulmonary artery and displacement toward the right. The electrocardiogram was abnormal but of a nonspecific pattern. The patient was fibrillating at a rate of 70. We are not told whether she was digitalized or not. The changes in the T waves and ST segments could have resulted from digitals, or they could have represented some degree of coronary disease. Absence of left-axis deviation and of an upright T wave in Lead CF, are against hypertensive strain. Absence of right-axis deviation is against cor pulmonale. The one blood pressure reading given was essentially normal, but this was after a debilitating illness and the patient may have had an elevated pressure earlier. The x-ray appearance is not that of a hypertensive heart. With a pulse of 70 and flat, quiet breathing, I cannot believe that any important degree of congestive failure was entering into the picture, although we are told that she was placed on a low-salt diet. The presence of a thick, dry skin is noted, and yet the eyebrows were full. Sparse pubic and axillary hair need not be too significant in a woman seventy-three years of age. Again, a heart rate of 70, with a temperature of 100°F, especially if she were not digitalized, is extremely significant. I cannot but wonder if the patient had myxedema. In a study of patients with myxedema at this hospital a few years ago,<sup>1</sup> fairly marked cardiac enlargement was usually found, often simulating the water-bottle variety, and all types of T-wave variations occurred, often, but not always, with low voltage and with either a normal axis or left-axis deviation. In none of the cases studied here or reviewed in the literature was

auricular fibrillation found, even in those with hypertension, which was frequent. If this patient had myxedema, I should consider that she had some other form of heart disease. With a history of myocarditis of twenty-nine years' duration, together with the presence of auricular fibrillation and the absence of left-axis deviation and chest pain, the possibility of an undetected mitral stenosis cannot be overlooked, regardless of a negative past history.

Finally, we come to the immediate cause of death. There was a sudden exitus preceded by moaning and short, gasping breathing. Was this acute myocardial infarction with ventricular fibrillation or acute pulmonary edema, or was it a massive pulmonary embolus? The description is not that of acute pulmonary edema. Apparently, the heart beat was heard to the end. I should expect death from acute coronary thrombosis to be either more rapid or more prolonged, with evidence of pulmonary edema. The cyanosis and moaning, as well as the short gasps, in a woman who was already assumed to have had phlebitis, sound more like a massive pulmonary embolus to me, and on that I shall rest.

DR TRACY B MALLORY: Has anyone another suggestion?

DR ALFRED KRANES: About fifteen years ago Drs. Mallory and Means<sup>2</sup> reported the case of a patient with phlebitis and thrombosis of the pulmonary artery. The x-ray picture in the case under discussion looks like the one in that case, although the clinical picture is different.

DR MALLORY: Your memory is better than mine, Dr. Kranes.

DR HELEN S PITTMAN: This woman was the fattest I have ever seen. The reason no pelvic examination was done is that she was a human mountain and could not move herself. It was impossible to get her into position. She did not notice that the leg was swollen because she did not see the leg. I discussed the case with Dr. Linton and thought that the picture was consistent with infarction and that the pulmonary emboli had occurred weeks or months before the local evidence of thrombophlebitis. We sent out an emergency call for the Peripheral Circulatory Service, which was answered by Dr. Faxon.

DR HENRY H FAXON: To me, this was an interesting problem because, as Dr. Pittman has said, the patient was not exactly an ideal candidate for surgery. Unless one had seen the torso, one could not possibly imagine what the situation was. Another point of real significance is that, having seen her, one would agree that there was no question that she had had a deep phlebitis in the past, and without much doubt she had a recurrence of the deep phlebitis in the present. The right thigh was markedly larger than the left. It has been our belief—also expressed by Ochsner<sup>3</sup> and others—that, if the thigh is swollen, the process of the deep

thrombophlebitis is marked enough and high enough and so adherent to the vessel that one is no longer faced with an indication for a femoral ligation. When we started to carry out this procedure in a few patients with swollen thighs, we exposed the femoral veins only to find that the clot was extremely adherent, and nothing was gained by the operation, the process had gone above that. In this case the question was therefore not whether I should do a femoral ligation, which I knew would be futile, but whether I should consider going high enough to do a ligation of the vena cava. That was not justified in any sense, being such a major procedure. As I have said, it is generally believed that if the thigh is swollen the patient is free of the danger of having a clot break loose. I made a note in the record dogmatically that at times large pulmonary emboli occur in patients with a swollen thigh either from another lesion above the point of attachment or from the unaffected leg. I did not consider myself justified in ligating the vein in this patient with deep phlebitis. The possibility of dicoumarol and heparin held only faint promise. The question always arises whether one should start therapy and keep anticoagulants going a long time until the patient can be mobilized again. It would have been a long time before this patient could have been active, so that I advised taking no surgical steps and only faintly encouraged the use of dicoumarol.

DR CLARK: Was she on digitalis?

A PHYSICIAN: She was not.

DR CLARK: Did you think that she had myxedema?

DR PITTMAN: No, we did not.

#### CLINICAL DIAGNOSES

Thrombophlebitis, right leg  
Pulmonary embolus

#### DR CLARK'S DIAGNOSIS

Massive pulmonary embolus

#### ANATOMICAL DIAGNOSES

*Pulmonary emboli, multiple, old and fresh*  
*Infarcts of lung*  
Chronic thyroiditis, slight  
Thrombophlebitis of right leg

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy was limited to a thoracic incision so that we cannot answer all the questions that we might like to. The major finding was in the pulmonary artery, which contained two distinct recognizable emboli: an old one, which was grayish-white and adherent, and a fresh one, which was coiled in the main pulmonary artery and its primary branches. The latter was unquestionably the immediate cause of death. There were two infarcts

in the right lower lobe, one of which was so old that its center had lost its blood pigment and had become almost white. The second, a small one near the base of the right lower lobe, was more recent.

The heart was slightly hypertrophied, weighing 410 gm. We could find nothing particularly wrong with it. The coronary arteries were in excellent condition, showing little arteriosclerosis. We were able to examine the thyroid gland, which was normal in weight and showed slight focal inflammation and a little adipose tissue inside the thyroid capsule, suggesting a mild degree of atrophy but not enough to produce a significant degree of myxedema. There were no clots in the venae cavae or in the iliac veins. When the legs were elevated and squeezed we could force out no blood from the right side, whereas there was a free flow from the left, so that there was no evidence of disease on the contralateral side.

DR CLARK: Can you explain the apparent shift of the heart to the right?

DR MALLORY: No, we found nothing to explain it. We were not impressed by the degree of atelectasis in the right lower lobe.

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#### CASE 33302

##### PRESENTATION OF CASE

A fifty-eight-year-old single Irish truck driver was admitted to the hospital for abdominal pain.

For five days the patient had had continuous pain, starting in the epigastrium and gradually spreading to involve the entire abdomen. The appetite had fallen off, but the bowels continued to move in their usual fashion, with the customary daily laxative tablet. He had no bleeding by rectum and no nausea and vomiting until the day of admission, when he vomited recently ingested food but no blood.

Seven months before admission the patient had been admitted to another hospital for pneumonia, with coughing, dyspnea, chills and fever. At that time physical examination revealed a slight elevation in blood pressure and an enlarged heart. He was started on digitalis, which was continued thereafter. Two weeks later he resumed work but developed increasing dyspnea and after three months was again hospitalized. At that time the ankles were not swollen, and he could usually lie flat in bed. On discharge about two weeks later he was improved but was able to work only a couple of days,

he subsequently became increasingly dyspneic and orthopneic, and the ankles began to swell.

He had been admitted to this hospital two months previously because of obvious congestive failure, with a blood pressure of 160 systolic, 98 diastolic. The thyroid gland was palpable but not enlarged. The heart was enlarged, the border extending to the anterior axillary line, and the pulmonic second sound was louder than the aortic. There were no murmurs, but a protodiastolic gallop was described by one observer. Moist rales were heard at both lung bases, and the liver edge was palpated three fingerbreadths below the costal margin but was not tender. The neck veins were only slightly distended. There was moderate ankle and sacral edema. The urine gave ++ and +++ tests for albumin. An electrocardiogram revealed sinus rhythm, a rate of 100, a PR interval of 0.18 second, a QRS interval of 0.12 second, a low voltage and a tendency to left-axis deviation, with a flat T wave in Lead I, low T waves in Leads 2 and 3, absent R waves in Lead CF<sub>1</sub>, slight elevation of the ST segments in Leads CF and CF<sub>2</sub>, an extremely small R wave in Lead CF<sub>3</sub>, a small notched R wave in Lead CF<sub>4</sub>, and upright T waves in Leads CF<sub>1</sub>, CF<sub>2</sub>, and CF<sub>3</sub>. X-ray films of the chest showed prominent pulmonary vascular markings and a much enlarged left ventricle. Another film a week after admission revealed only slight clearing of the bases and a patch of increased density in the right lower lobe, which was more prominent than that on the previous examination. The patient complained of some nausea and continued to be short of breath. He was discharged about three weeks after admission on bed rest, a low-sodium diet, diuretics and digitalis.

On physical examination the blood pressure was not obtainable, and the heart sounds were regular but extremely faint. There were rales at both lung bases but no evidence of consolidation. The abdomen was distended, spastic and diffusely tender, with almost no peristaltic sounds. Rectal examination revealed a tender pouch of Douglas but no distinct masses. Dark-red blood was noted on the examining finger. The heart did not appear enlarged to percussion. There was no ankle edema and only slight edema over the sacrum.

The temperature was 100.4°F, the pulse 90, and the respirations 48.

Examination of the blood revealed a hemoglobin of 14.5 gm, a white-cell count of 13,300 and a hematocrit of 43 per cent. The total serum protein was 6.7 gm per 100 cc. A plain film of the abdomen disclosed considerable distention of the small intestine and what appeared to be stomach, with no evidence of distention or retained fecal material in the colon.

Shortly after arrival the patient vomited reddish-black material, which gave a ++++ guaiac test,



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## WHAT ARE HOSPITAL SERVICES?

THE new contracts of the Blue Cross, which went into effect on June 1, have again raised the question concerning the definition of hospital services. These contracts call for a per-diem allowance that is identical in any one hospital but varies from hospital to hospital according to the services ordinarily furnished and to the actual charges for such services in 1946 adjusted to current rates. "Services ordinarily furnished" are considered to include x-ray diagnosis and treatment, anesthesia and laboratory work when such services are rendered by employees of the hospital. To this interpretation, however, the radiologists, anesthesiologists and pathologists who are connected with the hospitals on either a

full-time, part-time or percentage basis have taken violent exception. Indeed, various organizations of these three groups of specialists presented resolutions at the annual meeting of the Council of the Massachusetts Medical Society that opposed any arrangement by a hospital with the Blue Cross that permitted the latter to guide or determine professional services that criticized the per-diem allowance because it fails to distinguish between hospital and professional services and that recommended that all charges for professional services by physicians should be excluded from hospital-service contracts. These resolutions were adopted by the Council, with the recommendation that a committee be appointed to investigate the matter.

Are x-ray diagnosis and treatment, anesthesia and laboratory work true hospital services? Certainly the maintenance of the respective departments, including the cost of equipment, supplies and nursing and technical personnel, is a hospital expense and hence should be included as hospital service. And the same reasoning seems to apply to those physicians rendering professional services who are paid by the hospital. Thus, the tendency "to guide or determine professional services" and the failure "to distinguish between hospital and professional services" now rests — and has for many years — with the hospitals rather than with the Blue Cross. In fact, the per-diem method of payment to hospitals, with one exception, calls for no change in the financial arrangements between the hospitals and their medically trained employees; it is essentially a change in accounting methods whereby a great deal of detailed bookkeeping on the part of the Blue Cross, as well as by the hospitals, will be eliminated.

The "fly in the ointment" appears to be the statement by the Blue Cross that the new contracts cover all ancillary charges regardless of the status of the patient. Just why this provision was passed by the governing board of the Blue Cross and accepted by the hospitals is difficult to understand. Obviously, the Blue Cross has less authority — in fact, none — to determine professional charges to a private patient than it has to decide what such a patient shall pay for his room and board. But the allowance for the latter is limited to a certain

figure, the patient being billed for the balance. The same scheme is employed for subscribers to the Blue Shield whose earnings are sufficient to remove them from the low-income group. In other words, it appears that the private patient should be allowed a credit for such services but that he should be billed directly for all charges above a predetermined maximum. That semi-private and ward patients are entitled to unlimited services may seem unfair, but it is likely that the charges for these services, taking into consideration the financial status of the patient, would not often exceed the credit permitted to the private patient.

Although this one point directly concerns the Blue Cross, all other matters of the controversy appear to pertain to the hospitals and their medically trained employees. Possibly it is improper for hospitals to charge for services of this type, if so, drastic changes in organization must be made. In any event, the report to the Council of the committee appointed to consider the matter will be awaited with interest.

### THE TREND IN HEART DISEASE

It has been estimated that approximately 4,000,000 persons in the United States have heart disease and that the number of persons so afflicted not only has increased during the past two decades but is still on the increase.\* The number of cases has been growing principally because of the general aging of the population and to a lesser extent because of the increase in the total population.

There are, furthermore, occupational differences in cardiac patients that reflect, in part, the physical demands and the mental stresses of various trades. It is not surprising that bartenders have the highest mortality from heart disease, but it is not especially comforting to learn that physicians are but slightly less vulnerable. In addition, it is difficult to understand why barbers, who apparently work no harder than physicians and are certainly under less mental strain, should die of heart disease only slightly less often than bartenders and at virtually the same rate as physicians. Perhaps the tonsorial art is truly arduous.

Apart from the question of whether heart disease as a whole is on the increase, one must take into consideration the types of cardiac disease from which people die, as well as the changing diagnostic criteria during the past twenty-five years. If this is done, one learns that deaths ascribed to chronic valvular disease have shown a steady and rather rapid decline whereas those due to disease of the coronary arteries have made a corresponding — and alarming — increase. It must, however, be remembered that the clinical diagnosis of coronary disease has only recently achieved its present accuracy, and yet autopsy figures tend to show that there is not only a relative but an absolute increase in the mortality rate from this type of heart failure.

Regarding prognosis, the death rate from chronic valvular disease in cases of rheumatic fever with no heart involvement during the first year after the attack is comparatively low, being only 25 per 1000 for boys. With cardiac involvement, the rate is materially higher, being 208 per 1000 for boys. In general it may be said that the death rates for boys and girls following rheumatic fever are approximately the same except that during the first year of illness — whether or not the heart is reported to be enlarged — the mortality among boys is considerably greater than that among girls. Although the immediate mortality of coronary thrombosis is close to 20 per cent, it is encouraging to learn that five years after the initial attack over 50 per cent of those so stricken are able to carry on their work on either a full-time or part time basis. The worst prognosis appears to be in cardiovascular syphilis, which, theoretically, at least, is preventable.

On the whole the picture is not entirely black, for if one corrects for the aging of the population one finds that the over-all mortality from cardiac disease is not materially higher than it was thirty years ago, and that there is little that can be done about growing old — whether that be good or bad.

### MASSACHUSETTS MEDICAL SOCIETY

#### DEATH

MORRILL — Herman A. Morrill M.D. of Gardner, died on May 28. He was in his forty ninth year.

Dr. Morrill received his degree from University of Vermont College of Medicine in 1925.

\*Armstrong, D. B., Bonnett, E. C. and Dublin, L. I. *Studies in Heart Disease*. 20 pp. New York: Metropolitan Life Insurance Company, 1946.

## A HUNDRED YEARS AGO

At 10 o'clock, on Wednesday last, the Fellows of the Massachusetts Medical Society met for the transaction of the usual business. At 1 o'clock, Dr John Ware, of Boston, delivered the annual discourse, which was replete with wisdom and practical good sense. The dinner was served in Faneuil Hall. Not far from four hundred medical gentlemen dined as though they enjoyed the meal — Dr Henry Bryant suggests from Paris the possibility of a fatal result being one of the *remote sequelae* of the inhalation of ether — a fact, if such it proves to be, that has not been previously stated. He reports the case of a patient who died on the fourth night after operation, having presented no particular symptoms except pain in her back and a little crepitous rale in the lower part of her back, but no dullness on percussion. On examination, the lungs presented posteriorly a little hypostatic congestion, the bronchi were remarkably flaccid and slightly red. He suggests that if similar cases occur, attention should be directed to the lungs — A great deal has been said of late by the secular press about *ship fever*. The famine in Ireland has hurried the rapid tide of immigration into this country, bringing a famishing multitude, crowding the steerage of every packet and passenger vessel, on board of which many have suffered for want of food and even of water, while occupying filthy and unventilated apartments. A malignant and fatal fever has thereby been generated on board ship, of which many have died on the passage, while still more have been landed either already sick or so infected by the atmospheric poison that they soon develop it, in a form no less dangerous and fatal than that which has proved mortal on board the vessels which brought them hither. In the nature and character of this fever there is nothing new or peculiar, its type is found to vary, but a large majority of the cases are well characterized under the name of *typhus petechialis*. The conditions of recovery are cleanliness, pure air, with ventilated apartments and careful nursing. Medication of an active character is contraindicated — The *New York Medical and Surgical Reporter*, which has been published weekly in that city for a short time, has been discontinued. The *Boston [Medical and Surgical] Journal* is again alone in this country as a weekly visitant to the medical profession — Among the numerous readers of this journal, there must be many who have patients laboring under long-continued disease whom they would desire to send to the Saratoga Springs, but are deterred by the expenses. Many private houses charge only from \$4.00 to \$7.00 a week and there are three large and excellent establishments, which comprise all necessary comforts and conveniences and afford nearly as good tables as the most expensive hotels, where the charge for board and lodging is \$5.00 for a week. There are quite a number of houses which have

the sign "House Room" at the door. This implies that a party, containing one or more females, can be allowed lodging, room, bed, bedding and furniture, and permission to use the fire and cooking utensils of the family — all for \$1.00 a week to each individual — The Post Master, writing from Geneva, Coffee County, Alabama, says that among a population voting about eight hundred, and a Geneva containing about forty families, they cannot count *one doctor*. The village is on a stream navigable for steamboats, at the heart of navigation and in a cotton region — Died, Dr Collins, young and accomplished physician, of ship fever which was contracted in rendering voluntary professional assistance to Irish emigrants in the hospital — Extracted from the *Boston Medical and Surgical Journal*, June-July, 1947

R I

## MISCELLANY

### NEW ENGLAND DIABETES ASSOCIATION

At the first annual meeting of the New England Diabetes Association, held at the Boston City Hospital on April 11, the following officers and directors were elected: president, Dr Elliott P. Joslin, vice-president, Dr W. Richard Ohle, secretary, Dr James H. Townsend, treasurer, Dr Helmut Ulrich, and directors — to serve for one year, Drs F. Gorham, Brigham, John Casey, David Hurwitz and Augustine Conroy; to serve for two years, Drs Howard F. Root, Alexander Burgess, Harry T. French and E. R. Blaisdell, and to serve for three years, Drs Frank N. Allan, George Ballantyne, Richard Stetson and Ellsworth L. Amidon.

The Board of Directors held a meeting on May 14 to consider plans for the future operation of the association. It was voted to hold two meetings a year, in addition to the annual meeting, one of which would be held outside of Boston. Committees were appointed to report on various problems concerning the welfare of diabetic patients. The following honorary members were unanimously elected: Drs Full Albright and George R. Minot and Miss Frances Stern.

At present the association comprises 105 active members and 3 honorary members.

It is anticipated that the next annual meeting of the association will take place in Providence during the first two weeks of November.

## NOTICES

### AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

The First International Congress on Mental Deficiency will be held in Boston, at the Hotel Statler, on May 11, 13, 14 and 15, 1948. This meeting is to commemorate the first American institution for mental defectives, which was established in Boston in 1848. It is anticipated that there will be delegates and speakers from North and South America, the British Isles, Europe, Australia and New Zealand. The chairman for the Committee on Arrangements is Dr Stanley Raymond, of Wrentham, Massachusetts.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JULY 31

FRIDAY, AUGUST 1  
\*10:00 a.m. - 12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital

MONDAY, AUGUST 4  
\*12:15 - 1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital

WEDNESDAY, AUGUST 6  
\*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital

\*Open to the medical profession

(Notices continued on page xiii)

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Number 5

## THE OPERATIVE TREATMENT OF DECUBITUS ULCER\*

EDMUND J. CROCE, M.D.,† AND MAJOR CHARLES H. C. BEAKES, M.C., A.U.S.

SINCE the original report on the operative treatment of decubitus ulcer from this hospital,<sup>1</sup> considerable experience has been amassed, and a great impetus has occurred in this field in other Army hospitals. Most of the work has been done on paraplegic battle casualties.<sup>2</sup> The indications for the operative closure of decubitus ulcers in these patients no longer appear to be disputable. First and foremost, such a procedure effects, with little risk, a tremendous boost in the patient's morale and suddenly terminates the loss of tissue protein from the ulcer surface, thus favoring protein anabolism, increased appetite, strength, weight and general well-being.<sup>3</sup> It also removes the stigma of dependency on frequent dressings and allows an unhampered progress in ambulation.

### GENERAL CONSIDERATIONS

The present report comprises the entire program of the management of decubitus ulcers in 130 paraplegic patients treated at Halloran General Hospital over a fifteen-month period, beginning in April, 1945. In this group were 62 patients with sacral ulcers, of which 42 were operated on at this hospital. Sliding, full-thickness flaps were employed in 38 cases, and split-thickness grafts in 4. The ulcers had been closed at other hospitals in 3 cases, by a rotating pedicle flap in 1 and by split-thickness grafts in 2. One of the last proved entirely unsatisfactory and was excised and replaced by sliding flaps. The ulcers in the remaining 17 cases were allowed to heal by secondary intention, either because they were small and superficial or because they were almost completely healed when the patients were transferred to us.

There were 49 cases of trochanteric ulcer. Of these, 31 were closed at this hospital by sliding, full thickness skin flaps. Eight had been closed at other hospitals—4 by sliding flaps, 1 by a rotated pedicle flap, and 3 by split-thickness grafts. Two of these cases proved rather unsatisfactory because of repeated ulcerations, and one has already been excised and replaced by sliding, full-thickness flaps.

There were 9 cases of ulcer of the ischial tuberosity. Only 4 of these patients were operated on.

There were a number of miscellaneous ulcers in the following order of frequency over the calcaneus, dorsal spines, anterior superior iliac spines, fibular head, scapular spines, malleolus and patella. Only an occasional case was selected for operative closure—2 over the dorsal spine, 1 over the anterior superior iliac spine, 1 over the scapular spine, 1 over the patella, and 1 of the anterior chest wall.

The objectives of the program were twofold: to obtain an early and complete closure and to obtain a closure that would be stable and satisfactory. Although the first objective could be readily realized by the application of split-thickness grafts to the denuded areas, it was soon observed that the end results thus obtained were often unsatisfactory. These grafts, which were intimately adherent to the underlying osseous prominence, with only a thin layer of fibrous tissue intervening, ulcerated repeatedly in response to the unavoidable trauma of the denervated skin. The grafts served as an expedient to obtain the first objective in patients who were not ready for the more extensive procedure, but the second objective was not considered to have been achieved, and these grafts were sometimes replaced by full-thickness flaps at a later date.

The preparation of a patient for the major procedure of closure with full-thickness skin flaps must receive careful consideration. The larger the ulcer, the more extensive the dissection of adjacent skin area to mobilize the skin and to close the defect without tension. Some degree of shock is unavoidable, even with transfusion, in the closure of large ulcers. Consequently, debilitated patients should not be subjected to such major procedures. Furthermore, the healing powers of such patients are poor, and they have less resistance to infection. The average paraplegic casualty was found to have lost about 50 pounds in weight the first month after injury. During this period of rapid and severe catabolism, when the protein stores of the liver and muscles were seriously depleted, most of the decubitus ulcers appeared—a great many of them within a few hours or a few days after injury. Although the appearance of the ulcers over bony

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†Assistant surgeon, Worcester City Hospital, Worcester, Massachusetts; formerly chief of Surgical Service, Halloran General Hospital.

prominences could in many cases be attributed to infrequent change of position and soiling during the rapid chain of evacuation from the front, in the last analysis it is likely that the skin is rendered more vulnerable to such traumas by the general catabolism, especially of proteins<sup>3</sup>

Clinically, during this early phase, the appearance of the decubitus ulcer is characteristic. There is no

closed by the temporary expedient of application of a split-thickness graft, since in most cases the patient is not prepared systemically for a major procedure. Many patients did not arrive at our hospital until several months had elapsed, and they had therefore passed successfully through the initial phase. Few of them, however, had been detained in the chain of evacuation long enough for skin grafts

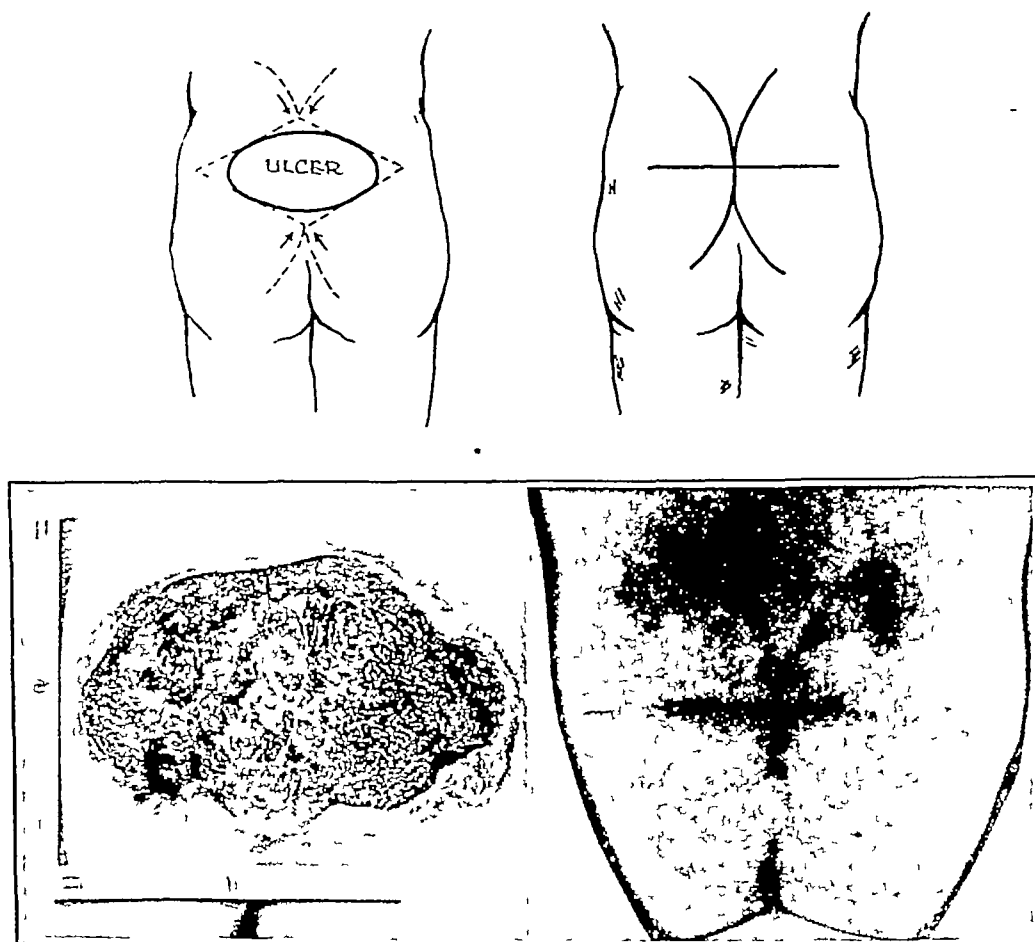


FIGURE 1 Transversely Oval Sacral Decubitus (Case 1)

The photographs show the appearances before and thirteen months after operation

evidence of healing process, but only of extending necrosis. The exudation of body fluids is profuse and thus, by a vicious circle, delays recovery. During this phase, treatment must be aimed at restoration of protein anabolism, forced oral feeding and parenteral alimentation with amino acids being used if necessary. Local infection must be controlled by conservative débridement of necrotic tissue and by systemic and local administration of chemotherapeutic agents. Anemia is controlled by repeated transfusions.

As soon as the local condition permits, as indicated by cessation of spreading necrosis, the appearance of healthy granulation tissue and the subsidence of active cellulitis, we believe that the ulcer should be

to be applied. The ulcers that most of them presented on admission were in the healing phase—that is, they were largely lined with a layer of granulation tissue, showed evidence of varying degrees of wound retraction and revealed only small areas of exposed nonviable or necrotizing fascia. Local acute inflammation had subsided, and exudation had materially decreased. The patients had already begun to regain weight and strength, they had passed the period of spinal shock, and automatic reflexes could be readily elicited. On admission, both aerobic and anaerobic cultures were taken routinely from ulcer surfaces. These cultures revealed a marked similarity to urinary and fecal flora, the following organisms being encoun-

tered *Proteus vulgaris*, *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, streptococcus and finally some of the Clostridia, usually of low pathogenicity. Other anaerobes were rarely found. On the basis of experience bacteriologic findings were, in general, disregarded although an attempt was made to protect the patient from invasive organisms by local dusting

dence of retraction from healing and finally showed invasion by a gray-white peripheral zone of proliferating epithelium.

Most patients required no anesthesia at the time of operation, since the ulcer occurred well below the sensory level. When anesthesia was required, endotracheal administration of ether was used almost exclusively, since it was considered safest

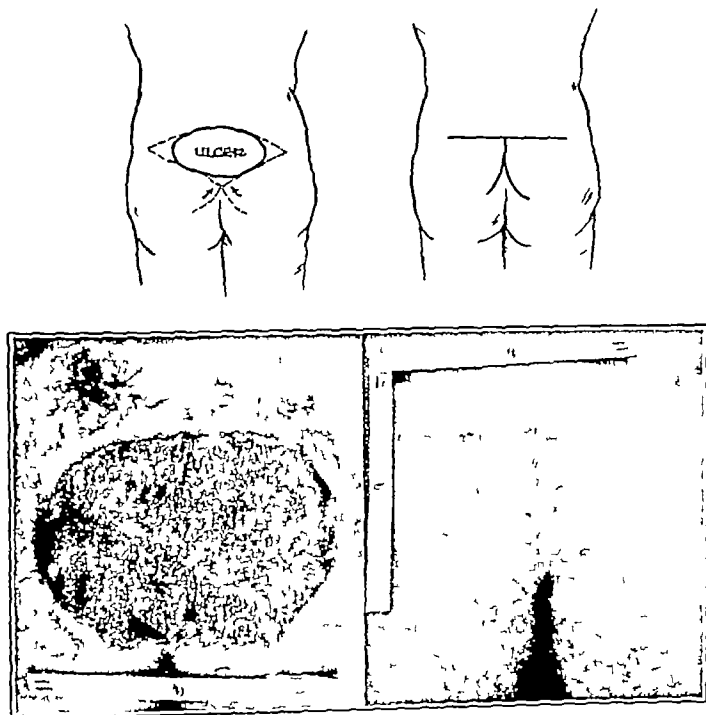


FIGURE 2. Transversely Oval Sacral Decubitus (Case 2)  
The photographs show the appearances before and five weeks after operation

of the operative surface with plasma-penicillin powder and by the administration of penicillin for five days preoperatively and, when indicated by the presence of *Staph. aureus* or streptococcus, for several days after operation. In the selection of patients for the major operative procedure, more reliance was placed on the clinical appearance of the ulcer. An ulcer was considered ready for operation when it became free from all evidence of recent cellulitis, when it presented a healthy granulating surface, when all non-viable tissue had separated, when exudation had practically ceased and when the wound margins began to show evi-

dence of retraction from healing and finally showed invasion by a gray-white peripheral zone of proliferating epithelium. Continuous spinal anesthesia was rarely employed. When only the proximal part of the ulcer lay above the sensory level, this portion of the operative field was sometimes infiltrated with procaine. The general operative technic has been described in a previous paper,<sup>1</sup> but the following technical details should be re-emphasized: sharp dissection, excision of all scarred tissue, fine-silk hemostasis, the development of flaps sufficiently extensive to allow closure without tension, thorough irrigation of the operative-wound surface with physiologic saline solution before closure, followed by dusting with plasma-penicillin

prominences could in many cases be attributed to infrequent change of position and soiling during the rapid chain of evacuation from the front, in the last analysis it is likely that the skin is rendered more vulnerable to such traumas by the general catabolism, especially of proteins.<sup>3</sup>

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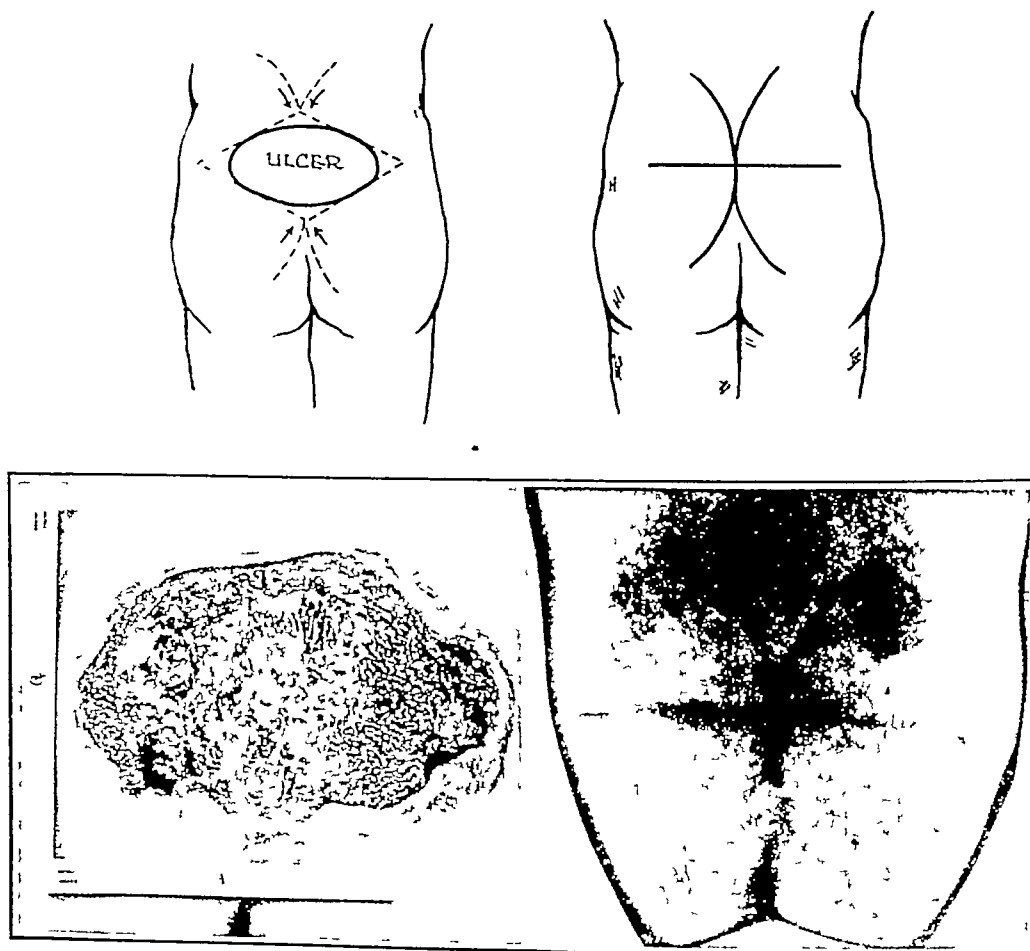


FIGURE 1 Transversely Oval Sacral Decubitus (Case 1)  
The photographs show the appearances before and thirteen months after operation

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like extensions over the posterior superior spines, were closed by a modification of the first method, the upper sector flap being smaller than the lower (Fig 3)

There were 6 vertically oval ulcers, which were closed by elliptical vertical excision, with triangular extensions into each buttock (Fig 4)

Of the small sacral ulcers, only one was closed by rotation of a single flap upward from one buttock

the four flaps in 5 cases, but these were all 2 cm or less in diameter and healed uneventfully in a few weeks. There was only one frank wound infection, and this significantly occurred in the only case in which absorbable gauze was used for hemostatic purposes. The infection subsided promptly on removal of the foreign body. We do not desire to condemn the use of this gauze, but merely to caution against its use immediately underlying a

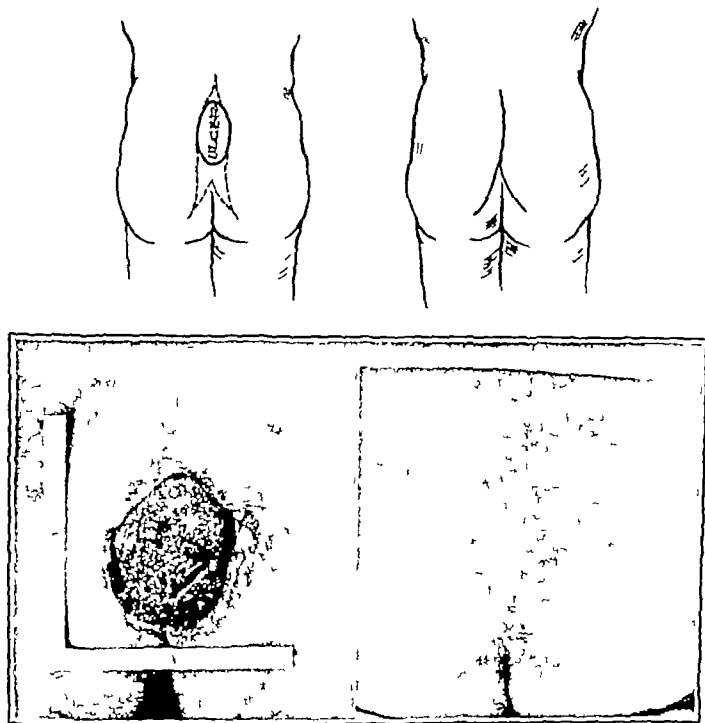


FIGURE 4. Vertically Oval Sacral Decubitus (Case 4)

The photographs show the appearances before and fourteen months after operation

(Fig 5) Although this method has been mentioned by other authors, it is not considered suited to the closing of large sacral ulcers

There were few serious complications. Only 1 patient developed a postoperative skin necrosis, resulting in a loss of an area 2 by 4 cm, which was surgically excised and successfully skin grafted. There were 2 cases of extensive wound disruption, but both healed by first intention on resuture. There were small dehiscences at the confluence of

suture line, particularly where there is a subcutaneous bony prominence. Sacral cases sometimes presented accumulations of sterile serous fluid that were treated by repeated aspirations. Drains were not used at any time in the entire series. One case developed a large hematoma underlying the flaps, and this was evacuated surgically.

Many of the sacral operations were performed more than a year ago. There have been few late complications. One patient developed an ischemic



necrosis of a portion of a postoperative flap three weeks after operation, owing to sitting in a wheel chair for six hours without a change of position. Another developed a secondary ulcer six months

ulcer would be a much more difficult accomplishment. An analysis of the situation discloses the nature of these difficulties. Thus, the skin is usually drawn tightly over the hip, so that more extensive

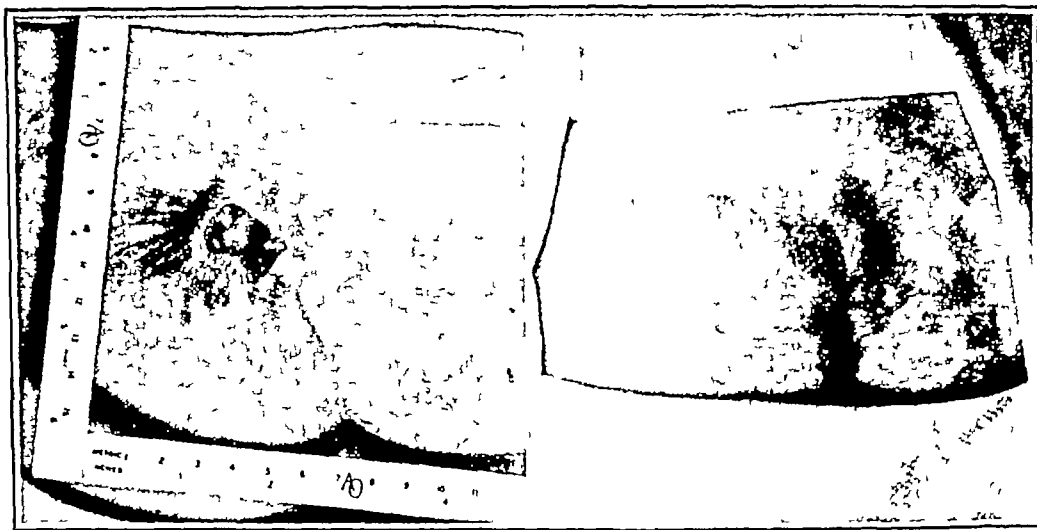


FIGURE 5 Small Sacral Decubitus (Case 5)

*The photographs show the appearances before and eleven weeks after closure by rotating a single flap from the buttock*

postoperatively, following immobilization for three days because of serious illness. The ulcers in both cases were closed by further advancing of the same flaps. These cases merely illustrate that the skin

dissection is required to cover relatively small defects. It is difficult to immobilize the hip without placing the patient in a plaster spica. Any motion of the hip — especially flexion and adduction, which



FIGURE 6 Small Trochanteric Decubitus (Case 6)

*The photographs show the appearances before and three months after linear closure*

must receive the same care postoperatively as the unbroken skin.

#### TROCHANTERIC ULCERS

From the beginning of the program, it was recognized that the successful closure of a trochanteric

are frequent in reflex spasms — tends to disrupt the repair of soft tissues over the trochanteric prominence. The superficial appearance of the ulcer generally belies its true extent, since there is usually considerable skin retraction about the ulcer and an extensive subcutaneous defect where the trochanter

has worn away the fascia lata to produce a so-called "false bursa"

A total of 49 cases of trochanteric ulcer have been observed in 43 patients. Thirty-one of these were operated on at this hospital. In 4 cases the ulcer had been closed before admission to this hospital. One of these had been closed by a rotating full-thickness flap, the donor site being covered by a split-thickness graft, this procedure proved quite

subsection, to raise a substantial anterior and posterior flap, usually allowed the approximation of these flaps without undue tension (Fig 6)

*Single sliding flap* Trochanteric decubiti over 3 cm but less than 6 cm in the transverse diameter could usually be closed by the sliding of a semicircular flap from the corresponding buttock. The incision was usually continued from the inferior angle of the ulcer medially and posteriorly

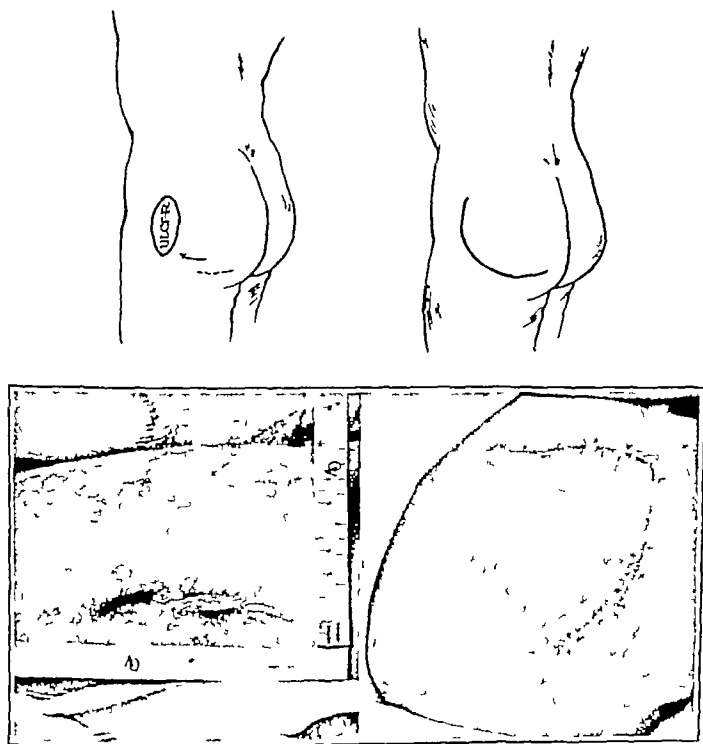


FIGURE 7 Trochanteric Decubitus (Case 7)

The photographs show the appearances before and four months after closure by the single flap method

satisfactory. The ulcers in 3 other cases had been closed merely by the application of split-thickness grafts, which proved rather unsatisfactory. One was finally excised and covered by a full-thickness flap. In general, the operative methods we employed fell into three groups

*Linear closure* Trochanteric ulcers are usually vertically oval. For those less than 3 cm in the transverse diameter, elliptical excision of all scar tissue along with the granulation tissue base and

along the inferior gluteal fold. A single large flap was developed and rotated laterally to cover the defect (Fig 7)

*Double sliding flaps* Trochanteric ulcers over 6 cm in the transverse were closed by the development of an additional semicircular flap anteriorly and superiorly from the anterior surface of the thigh, thus creating an S-shaped wound on approximation (Fig 8)

In this series 5 patients were treated by linear closure, 20 by single sliding flaps, and 6 by double sliding flaps. In general the results were not so good as those in the management of sacral ulcers. Of the ulcers with linear closures, 3 healed by first intention, and 2 developed small dehiscences. Of the 21 single-flap closures, 13 healed by first intention, and 4 developed partial dehiscences. Three of

ischial regions were encountered with greater frequency. Most paraplegic patients have atrophic gluteal muscles, as a result of which they present a great deal of loose skin for the closure of sacral ulcers, but little padding for the ischial tuberosity. Clinically, these patients sometimes developed redness and swelling in the ischial regions. At first these lesions were often mistaken for early ischial

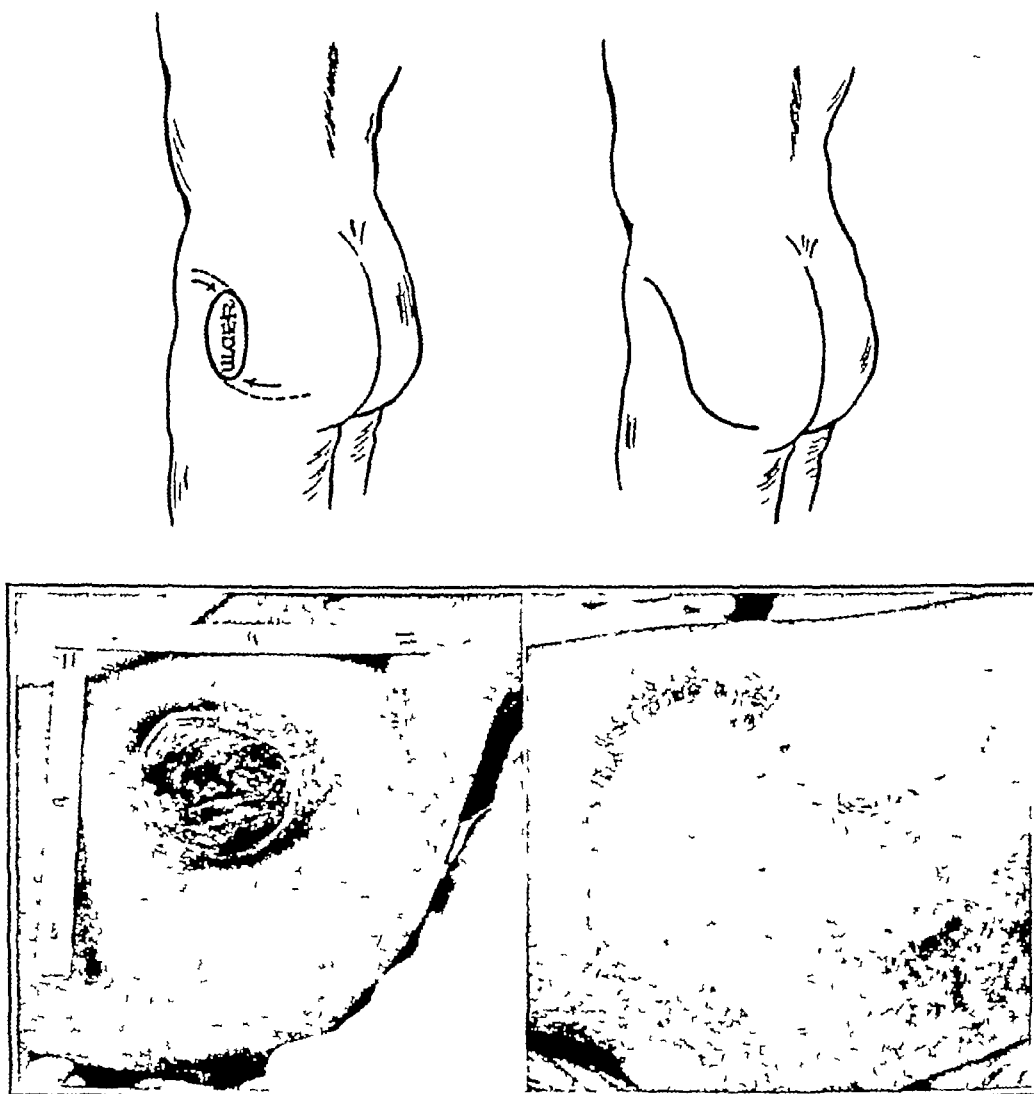


FIGURE 8 Trochanteric Decubitus (Case 8)

*The photographs show the appearances before and two months after closure by the double-flap method*

the latter patients were severely spastic, and another was undernourished and failed to heal any of his operative wounds. It is believed that postoperative immobilization in a padded plaster spica, with the hip abducted, will improve the results in this type of surgery.

#### ISCHIAL DECUBITUS

As the program of rehabilitation of paraplegic patients progressed and more of them left their beds for the wheel chairs, various lesions of the

abscesses, but it was soon discovered that incision led to the formation of sinuses communicating with chronically infected ischial bursas, curable only by excision of the bursa. Preferably, the early treatment consists of cessation of weight bearing and systemic chemotherapy. The signs of inflammation usually subsided slowly with this regime. Once the superficial tissues have ulcerated over the ischial tuberosity, however, the ulcer is best treated surgically by excision and linear closure. So important is complete immobilization in the postoperative treat-

ment of these lesions, that we have come to rely on nothing short of the well padded plaster spica. Of the 4 patients operated on, 2 with ulcers that healed by first intention were thus treated.

### MISCELLANEOUS TYPES

A relatively frequent decubitus that continues to challenge the surgical program is that over the calcaneus. From our own experience and that of others, it was concluded that split-thickness grafts would be undesirable. Local closure with full-thickness sliding flaps was also not feasible, and pedicle flaps from the thighs were considered impractical. The patients were therefore treated by nonoperative methods and not allowed to delay ambulation.

In the closure of dorsal ulcers, it seems advisable to resect the protruding spinous process before closure.

### SUMMARY AND CONCLUSIONS

The treatment of large decubitus ulcers in a young paraplegic patient is a surgical problem.

The more frequent varieties of decubitus ulcer—sacral, trochanteric and ischial—may be closed by sliding full-thickness skin flaps. Surgical experiences in performing such closures on a large number and variety of ulcers are reported. The important details of these procedures are presented.

Full-thickness skin closure of decubitus ulcers gives a much more satisfactory result than either secondary healing or closure with split-thickness graft. The procedure is sometimes a relatively formidable one, and is not recommended for the closure of decubitus ulcers in the aged and debilitated.

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## WOUND INFECTIONS WITH FRIEDLÄNDER BACILLUS FOLLOWED BY MENINGITIS

SAUL SOLOMON, M.D.\*

NEW YORK CITY

THE Friedländer bacillus (*Klebsiella pneumoniae*), under the right conditions, is highly virulent for man. Hence, although infections with this organism are not frequent, they deserve consideration out of proportion to their incidence. Appreciation of this fact is essential so that cases may be recognized and treated early with methods now in use and also in order that new and more effective remedies may be developed. With this in mind, 3 cases of wound infection with Friedländer bacillus, followed by fatal meningitis, are presented below.

There are surprisingly few reports in the literature containing careful bacteriologic studies of wound infections and only a few bare references to the role of the Friedländer bacillus. Riggenbach<sup>1</sup> was perhaps the first to report a case of wound infection due to the organism. Levaditi,<sup>2</sup> reporting on wound infections in World War I, mentioned that the organisms most generally found were staphylococci (in 85 per cent of cases), Friedländer bacillus, *Clostridium welchii*, streptococci, the coli group and *Pseudomonas aeruginosa*. Pulaski, Meleney and Spaeth<sup>3</sup> found that staphylococci could be recovered from nearly every wound. Streptococci were isolated from half the wounds. Gram-negative organisms, such as *Escherichia coli*, *Proteus vulgaris*, *Eberthella typhosa*, *P. aeruginosa* and *K. pneumoniae*, were found in

a fourth of the cases. Among the numerous other reports on wound infections there is to my knowledge no mention of the Friedländer bacillus. The First General Medical Laboratory, which received a fair sampling of cultures from United States Army hospitals in the United Kingdom, informed me in October, 1944, that within several weeks they had identified the bacillus in wound cultures in 6 cases. It is my impression that if careful cultures of wounds were done routinely, the bacillus would be found quite frequently. Its seeming rarity in wound infections may also be explained in part by the tendency to pass off all gram-negative rods found in wound cultures as coliform organisms.

Meningitis due to Friedländer bacillus is apparently rare. In 1938 3 cases secondary to pneumonia were reported.<sup>4</sup> Ransmeier,<sup>5</sup> in 1943, reported 1 case and referred to 29 others in the literature. In approximately half the cases the meningitis followed infections of the middle ear or sinuses. In the remainder it followed pneumonia, cholecystitis or colitis with bacteremia. None of the cases were related to trauma. Hence the finding of 3 cases of meningitis due to Friedländer bacillus following war wounds seems worthy of reporting.

### BACTERIOLOGI

The organism is a gram-negative rod, 0.5 to 5 microns in length and approximately half as wide

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Consequently, it may be either quite long or coccoid in shape. It may be seen singly or in short chains. It is nonmotile, nonspore forming, aerobic and facultative anaerobic. It has a distinct, thick capsule, which is seen on direct smears from infections with the organism. The organism grows readily in the usual laboratory mediums. On solid mediums the colonies are large and opaque and have a slimy, mucoid appearance.

Julanelle<sup>6</sup> identified several distinct types by means of agglutination and animal protection tests. These are groups A, B and C, as well as a heterogeneous group known as "X." The distinction between the different types depends on chemical differences in the polysaccharide of the capsule. The organism has a rather wide distribution, being found in the soil, air and water. It also occurs as a saprophyte in the upper respiratory and intestinal tracts in a small percentage of normal human beings.

Infections due to the bacillus may be conveniently divided into pulmonary and extrapulmonary groups.

#### PULMONARY INFECTIONS

Approximately 1 to 3 per cent of all pneumonias are due to *K pneumoniae*. This form of pneumonia is most virulent, but many cases run a course with a temperature below 101°F.<sup>4</sup> The pneumonia is lobar in character, but involvement of several lobes is frequent. The sputum, in the majority of cases, is a characteristic homogeneous emulsion of blood and mucus—brick red in color and unlike the prune juice sputum of pneumococcal pneumonia or the bloody sputum often found with tuberculosis. A direct smear shows many large, gram-negative encapsulated bacilli. The organism can be recovered in pure culture by mouse inoculation or by culture of the sputum on blood-agar plates. Bacteremia occurs in the majority of cases but is ordinarily not intense. The most frequent complications are abscess formation and empyema, meningitis and purulent pericarditis occur more rarely. The mortality in untreated cases is over 90 per cent.

Chronic lung infections due to this organism are less frequent and are often misdiagnosed.<sup>7</sup> Non-putrid lung abscesses are frequent, and these are usually located in one or both upper lobes. Hence, the disease is often mistaken for pulmonary tuberculosis unless the case is critically evaluated. It is by no means easy to find the organism in the chronic stages, since secondary invaders may overgrow it.

#### EXTRAPULMONARY INFECTIONS

These have been described in detail by Baehr, Schwartzman and Greenspan<sup>8</sup> and more recently by Jaffe.<sup>9</sup> Intra-abdominal infections are usually secondary to perforative lesions of the large intestine, such as appendicitis, diverticulitis and carcinoma. Abscess formation or generalized peritonitis may occur. Secondly, subphrenic or liver abscess and, occasionally, septicemia may result. Biliary-

tract infections, which are next in frequency, usually occur in association with gallstones. Purulent cholecystitis and mastoiditis are not rare and may lead to cavernous sinus thrombosis or meningitis.

It is of interest that extrapulmonary infections generally have a relatively low mortality (17 per cent). The mortality in cases complicated by bacteremia is about 75 per cent, and that by meningitis is over 90 per cent.

#### TREATMENT

Specific horse antiserum has been used with varying results. Bullowa, Chess and Friedman<sup>10</sup> report a reduction of mortality in pneumonia due to Friedländer bacillus, but my own experience with serum was disappointing.<sup>4</sup>

In recent years the sulfonamides have been used with some success. I<sup>7</sup> first employed sulfapyrimidine in 1938 in the treatment of 4 cases. The patients survived, although they developed the chronic form of the disease. More recently, Feinstone and co-workers<sup>11</sup> showed that in experimental infection in mice, sulfadiazine is superior to other sulfonamides, and clinical reports have described the same results. Appelbaum<sup>12</sup> noted recovery in a fair percentage of cases of meningitis treated with sulfonamides and, more recently, in a case treated with streptomycin. Penicillin has not been found effective.<sup>13, 14</sup> In Cases 1 and 2 reported below, the organism was resistant in vitro to concentrations of penicillin as high as 1000 units per cubic centimeter—levels that are impossible to attain in the bloodstream. More hopeful, however, is recent experimental work by Heilman,<sup>15</sup> which indicates that streptomycin may have definite value.

#### CASE REPORTS

**CASE 1.** A 26-year-old soldier was wounded in France August 8, 1944, by mortar-shell fragments, sustaining penetrating wounds of the left buttock and a fracture of the ilium. He received treatment in a field hospital and was evacuated to England on August 20.

The wound of the left buttock showed a mucopurulent discharge, and treatment with sulfadiazine was instituted (1 gm. every 4 hours). On August 24 the temperature rose to 104°F, the neck was stiff, and Kernig's sign was positive. Cultures from the wound and blood were positive for *Typus K pneumoniae*. A spinal tap yielded a cloudy fluid containing 5200 polymorphonuclear cells per cubic millimeter, the sulfadiazine level was 3.8 mg. per 100 cc. A direct smear of the sediment showed many gram-negative, encapsulated bacilli. Examination of the blood showed a white-cell count of 14,800, with 82 per cent segmented neutrophils, 8 per cent young forms and 10 per cent lymphocytes.

Treatment with penicillin was started at 4 p.m., the patient receiving 30,000 units intravenously, followed by 30,000 units intramuscularly every 4 hours. At 6 p.m. 5000 units of penicillin was given intrathecally, followed by 5 gm. sodium sulfadiazine intravenously. The temperature rose to 107°F at 10 p.m. Analysis of the spinal fluid showed essentially the same findings, except that the sulfadiazine level was 9.3 mg. per 100 cc., 5000 units of penicillin was instituted intrathecally. The patient did not respond to therapy and died at 9 o'clock on the following morning.

**Autopsy.** Post-mortem examination disclosed greenish-yellow pus covering the entire brain and spinal cord. The choroid plexus contained a number of small collections of pus. Careful examination of the spinal cord revealed tear of the meninges.

Dissection of the wound of the left hip demonstrated a severe destructive process involving the deep muscles. The internal and middle ears appeared normal. Cultures from the meninges, the blood and the wound showed a pure growth of *K. pneumoniae*.

Case 2. A 19-year-old soldier was wounded by shell fragments on August 13, 1944 sustaining a scalp wound and fracture of the skull. He did well and was evacuated to England on September 6. The general condition was good, but the wound exuded some serous material. Roentgenograms of the skull showed several indurated bone fragments near the falx and a metallic foreign body at the base of the skull.

Operation was done for depressed skull fracture on September 9 devitalized brain and free bone fragments being removed. Two days later the patient developed signs of meningitis. A spinal tap yielded a purulent fluid that contained Friedländer bacilli in pure culture. The patient was treated intensively with sulfadiazine and penicillin intramuscularly and intrathecally but showed no response. Death occurring on September 13.

Autopsy. Post mortem examination showed the brain to be covered by a massive exudate of fibrin and pus that contained many encapsulated bacilli. A brain abscess was seen in the hypothalamus in the center of which a metallic foreign body was found.

Most of the left lung was consolidated in the stage of red hepatization. Culture of the wound, the abscess, the meninges, the left lung and the blood showed *A. pneumoniae*. It is of interest that the abscess had remained quiescent for 4 weeks before it ruptured leading to septicemia and meningitis.

Case 3. A 29-year-old soldier was wounded by shell fragments on September 9, 1944 sustaining penetrating wounds of the abdomen, with perforation of the jejunum and descending colon. He also suffered a deep laceration over the sacrum with fractures of the left transverse processes of the 3rd, 4th and 5th lumbar vertebrae. This was followed by left foot drop. The jejunal perforations were sutured and a colostomy was done at a field hospital. The patient received a blood transfusion, 20,000 units of penicillin and some sulfadiazine (quantity not stated) and was evacuated to England on September 28.

The temperature ranged from 99 to 102°F. He became restless and irrational. On October 1 a spinal tap yielded a milky fluid containing 90,000 polymorphonuclears per cubic millimeter. Gram negative encapsulated bacilli were seen in the smear and culture showed *K. pneumoniae*. Death occurred on the same day.

Autopsy. Post mortem examination revealed the laceration over the sacrum to extend into a large abscess 12 cm in diameter. The dura and several fibers of the cauda equina on the left were lacerated and beneath the pia a green purulent exudate was noted. A similar exudate was found over the cortex and base of the brain. The sinuses and middle ear were normal.

A small amount of green pus was expressed from around the apparently clean colostomy. The lungs showed several infarctions in both lower lobes and an embolus in one of the branches of the left pulmonary artery.

Culture of the heart's blood was negative; culture from the brain from the area about the colostomy and from the laceration in the sacral region showed *K. pneumoniae*.

The laceration of the sacral region involving the dura and cauda equina was apparently the site of an unrecognized Friedländer bacillus infection that had gained entry into the subarachnoid space resulting in meningitis.

## DISCUSSION

The patients in the cases presented above sustained shell-fragment wounds complicated by meningitis, but the pathogenesis of the meningitis was different in each case. In Case 1 the wound infection was followed by bacteremia and meningitis. In Case 2 there was a brain abscess around a shell

fragment. The abscess ruptured, resulting in meningitis and septicemia with death on the thirty-first day. The patient in Case 3 sustained lacerations of the sacral region and of the spinal dura. The wound was the site of *K. pneumoniae* infection that had extended directly through the torn dura leading to meningitis and death twenty-two days after injury. The organisms in Cases 2 and 3 were not typed, but their virulence and the finding of positive cultures in the blood and the meninges are presumptive evidence that they were Friedländer bacilli and not mucoid coliform organisms.

The origin of the Friedländer bacillus is in doubt. It is possible that the shell fragments carried the organisms into the tissues, but it is likelier that, in at least 2 of the cases, infection occurred during the period of hospitalization. This may have been due to fecal contamination, but since the organism is a frequent inhabitant of the upper respiratory tract it seems probable that the wounds became infected when dressings were changed. The wearing of masks by attending personnel and the strict observance of operating-room technique during routine dressings of wounds are often not practiced.

There were no features in the appearance of the wounds or in the clinical course that distinguish these cases from other wound infections. Such a differentiation could be attained only by routine bacteriologic study of infected wounds. Cultures were not made until an unusual complication had occurred. This was unfortunate because for some reason in each case a long latent period between the time of injury and the development of meningitis would have provided more time for treatment had the diagnosis of infection with Friedländer bacilli been made earlier.

The patient in Case 1 received adequate sulfadiazine therapy, but this did not prevent the development of bacteremia and meningitis. The addition of penicillin to the treatment after these complications had ensued had no effect. The second case was not diagnosed until forty-eight hours before death. Intensive therapy with penicillin and sulfadiazine had no effect. The patient in Case 3 was not given therapy for the infection.

## SUMMARY

Three fatal cases of wound infection with Friedländer bacillus followed by meningitis are reported. Meningitis in one case was secondary to bacteremia, in another, it was due to direct extension through the torn dura of the spinal cord, and in the third it followed rupture of a brain abscess surrounding a metallic fragment.

The origin of the wound infections is in doubt, although it seems likely that they represented cases of hospital infection, and the most important factor in hospital infection of wounds appears to be droplets from the nose and throat. Hence, the need for the

\*Performed by Lieutenant Colonel Jerome I. Silverman, chief of the laboratory of the One Hundred and Twenty-Third General Hospital to whom I am indebted for permission to publish this case.

wearing of masks by attending personnel and for the observance of strict operating room technic when wounds are dressed should be emphasized

Routine culture of wounds should be made as soon as infections are apparent. In this way the physician will have precise bacteriologic data and will be able to start treatment at once. Treatment with sulfadiazine and penicillin was unsuccessful in 2 cases. It would be rash to draw any conclusions from this, but on the basis of past experience and of reports in the literature, sulfadiazine appears to be the most effective agent in use at present. Newer antibiotics, such as streptomycin, give promise of greater effectiveness and should be given further experimental and clinical trial. In infections with such a virulent organism, however, no remedy will prove generally effective unless bacteriologic diagnosis is made early.

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ADDISON'S DISEASE ASSOCIATED WITH AMYLOIDOSIS FOLLOWING THERMAL BURNS\*

Report of a Case

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ADDISON'S disease associated with amyloidosis of the adrenal glands is uncommon, less than 20 cases having been reported. Amyloidosis of the adrenal glands accounted for about 2 per cent of the cases of Addison's disease reported by Guttman.<sup>1</sup> Amyloidosis following thermal burns has rarely been reported,<sup>2</sup> and Addison's disease associated with amyloidosis following burns has not been reported to our knowledge. The following case presented such a combination.

A 42-year-old Negroess with a noncontributory past history was admitted to the hospital May 10, 1944, with flame burns involving 15 per cent of the body surface, chiefly deep,

and severe thermal respiratory-tract injury. Eighteen hours after admission a tracheotomy was performed because of marked stridor and air hunger. There were no further respiratory difficulties, the tracheal tube being removed on the 10th day.

The surface burns were dressed initially with dry, sterile, pressure dressings without anesthesia or preliminary cleansing. Subsequent dressings were, for the most part, also dry-pressure dressings.

During the first 6 weeks the temperature varied between 100 and 102° F. Sulfadiazine, in doses of 6 gm. a day had been started on entry and was continued for 1 week. Following this 15,000 units of penicillin was given intramuscularly every 3 hours for 6 weeks. There were no toxic reactions to either drug.

Intravenous infusions of Amigen\* were started on the day after entry and during the first 2 weeks constituted the chief protein nutrient, 3000 cc being given daily. During that time the patient appeared to be in apparent positive nitrogen balance and to be maintaining her weight. The plasma protein concentration, however, fell from 7.2 gm. per 100 cc of plasma on entry to 6.3 gm., and the albumin from 4.2 to 2.8 gm. Oral administration of 225 mg. of ascorbic acid, 9 mg. of thiamine chloride, 6 mg. of riboflavin, 60 mg. of nicotinamide, 15,000 units of vitamin A and 3000 units of vitamin D was given daily, as well as 15 cc of crude liver extract (Wilson) intramuscularly.

During the 3rd week the intravenous infusions of Amigen were omitted, and the patient went into negative nitrogen balance, the intake having fallen to 6 gm. of nitrogen and 1600 calories daily. The vitamin intake remained the same. The plasma protein concentration, however, remained unchanged. By the 5th week, with urging and special nursing care, the intake was gradually raised to 40 gm. of nitrogen and 3500 calories daily, with dried beef serum as an oral supplement to the diet. The patient again appeared to be in

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\*Kindly supplied by Mead Johnson and Company, Evansville, Indiana.

positive nitrogen balance. The beef serum supplement was continued for 8 weeks. The vitamin intake was unchanged.

The hemoglobin which had been normal on admission fell to 55 per cent by the 5th day and remained between 55 and 60 per cent until the 7th week. Thereafter sufficient type-specific whole blood transfusions were given to maintain the hemoglobin between 80 and 95 per cent. In the 7th week skin grafting of part of the burned area by the Padgett dermatome technique was done for the first time and was repeated in the 8th and 11th weeks. The takes of the graft were good but the donor sites failed to epithelialize in the next 5 weeks. During this period the food intake declined and the patient lost weight and strength. The vitamin supplements were not changed. The temperature varied between 98 and 100°F.

In the 5th and 6th months, under a regime of special nursing care and forced feedings consisting chiefly of milk with added milk powder, sugar and Amigen, the patient's condition improved markedly. The vitamin intake remained the same. She gained weight and strength and was getting out of bed. The plasma protein and albumin concentrations, which had fallen to 5.4 and 2.4 gm per 100 cc respectively at the 8th week rose to 7.5 and 3.1 gm respectively. The tempera-

ture the level 2 hours after the injection of the insulin was significantly low, the fasting level being 98 mg and the 2 hour level 24 mg per 100 cc. On the 9th and 56th days, reactions were normal.

The urine, which since entry had shown albumin and white cells began to show large numbers of red cells in the sediment on occasional days during the 11th month. No casts were seen. The specific gravity of the urine became fixed at the end of the 12th month at 1.010. Urea clearance and phenolsulfonphthalein excretions were low. The non-protein nitrogen concentration in the plasma, which had been normal on entry and for the next 11 months rose to 49 mg per 100 cc in the 12th month (Table 1) and then rose slowly reaching a level of 75 mg per 100 cc by the end of the 12th month. The urine was negative for tubercle bacilli by the guinea pig technique, and a catheterized specimen was negative for other bacteria.

The blood pressure, which had been about 120/80 on entry, dropped to 105/70 by the 9th month and to 90/60 by the 12th month. The weight at that time was 90 pounds, as compared with an estimated weight of 125 pounds on entry. The granulations were still friable and grafting could not

TABLE 1 Pertinent Laboratory Data

HOSPITAL DAY	NONPROTEIN NITROGEN mg/100 cc	TOTAL PROTEIN gm/100 cc	CHLORIDE milliequivalents/liter	SODIUM milliequivalents/liter	CARBON DIOXIDE COMBINING POWER millimoles/liter	BLOOD PRESSURE
1	28	7.1	39	144	25	120/80
358	28	6.4	—	—	—	50/60
366	62	6.7	—	—	—	115/80
370	75	6.5	—	—	—	100/60
380*	118	—	68	128	—	70/40
381	98	—	84	—	13	110/50
385	87	5.1	60	135	16	—
386	78	5.5	—	—	—	95/55
390	118	—	—	—	20	100/65
391	60	—	100	—	—	95/55
393	67	5.0	69	—	25	100/65
395	78	5.0	75	—	26	82/50
397	70	5.0	100	136	22	104/50
401†	74	5.1	100	—	—	100/40
414‡	116	4.8	—	—	—	85/45
415	143	5.8	87	130	13	70/30

\*Diagnosis of Addison's disease in crisis, made at this time and adrenocortical extract, desoxycorticosterone, testosterone and sodium chloride therapy begun.

†Hormonal treatment discontinued.

‡Hormonal treatment resumed.

ture was normal and the donor sites had almost completely epithelialized.

From the seventh month on it was not possible to keep the patient on special nursing care. The food intake and general condition gradually deteriorated. In the 7th and 8th months 15,000 units of vitamin A, 3,000 units of vitamin D, 725 mg of ascorbic acid, 9 mg of thiamin, 6 mg of riboflavin and 1.5 cc of crude liver extract (Wilson) were given daily. In the 9th month through the 12th month the patient received in addition 2 cc of halibut liver oil with viosterol (Parke-Davis). Thereafter, the fat soluble vitamin supplements were omitted, and she was given 500 mg of ascorbic acid, 15 mg of thiamin, 20 mg of riboflavin and 150 mg of nicotinamide daily. Loss of strength and weight were marked. The donor sites and some of the grafted areas broke down. The granulations became exuberant and friable. The fever was low grade. Cultures of the wounds throughout the course showed hemolytic *Staphylococcus aureus* as the predominant organism, with alpha hemolytic and beta hemolytic streptococcus, diphtheroids and *Proteus vulgaris* also present in the majority of cultures.

In general the white-cell counts were elevated the majority being about 15,000 with occasional extremes of 8,000 and 30,000. The icteric index throughout was 4. Cephalin flocculation, hippuric acid bromsulfalein and Quick prothrombin determinations were made on several occasions during the first 7 months and were always within normal limits.

Intravenous glucose-tolerance tests demonstrated a significantly elevated blood glucose concentration 2 hours after the injection of 25 gm of glucose on the day of entry but a normal level on the 8th day. Intravenous insulin tolerance tests were done on the 1st, 9th and 56th days. On the 1st

day the patient was weak but alert. In the 13th month she became irrational and stuporous for a period of 6 hours following the administration of 0.1 gm (1 1/2 gr) of Nembutal. She had previously received this dose of Nembutal on many occasions without any untoward reaction. On the next day a dressing was done under cyclopropane anesthesia without preliminary medication. Following this she became delirious. The blood pressure fell to 85/40. On the following day she had an epileptiform seizure and became comatose. The blood pressure had fallen to 70/40 and the pulse was rapid and thready; the extremities were cold and clammy and the temperature 97°F by rectum. The plasma nonprotein nitrogen had risen to 118 mg per 100 cc, the chloride and the sodium which had been normal, had fallen to 68 and 128 milliequivalents per liter respectively. The carbon dioxide combining power on the next day was 13 millimoles per liter—it had been normal on entry. Pertinent laboratory data during the hospital course are presented in Table 1.

The diagnosis of Addison's disease in crisis was made by one of us (H. T.) and therapeutic measures were accordingly taken. Plasma and glucose in isotonic saline solution were given intravenously in the next hour. This produced a slight rise in the blood pressure to a level of 90/50 and a lowering of the pulse rate to 88. Immediately thereafter a regime of adrenocortical extract, desoxycorticosterone, testosterone propionate and additional intravenous saline solution and glucose was begun.

During the 1st day 50 cc. of adrenocortical extract, 35 mg of desoxycorticosterone and 50 mg of testosterone were given and 25 gm of sodium chloride and 300 gm of glucose were administered intravenously in the form of 10 per cent glucose in isotonic saline solution. Within 12 hours the patient had regained consciousness and had no further epileptiform



seizures. The blood pressure had risen by the following day to 110/50, and she was talking coherently. The rectal temperature had risen to 99°F. The blood sugar was normal. On the 2nd day 5 mg of desoxycorticosterone and 30 cc of adrenocortical extract in divided doses were given. The sodium and glucose intakes were about the same as on the previous day.

During the next 2½ weeks the patient received 25 mg of testosterone and 5 mg of desoxycorticosterone daily. She was given 2000 cc of Amigen with 300 cc of 50 per cent glucose intravenously daily, and was eating well. She appeared to be definitely improving. The blood pressure varied between 95/55 and 100/65. The nonprotein nitrogen had fallen to 60 mg per 100 cc, and the chloride had risen to

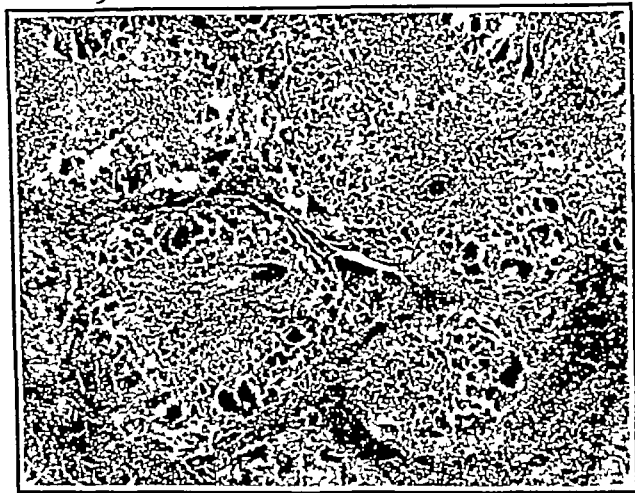


FIGURE 1 *Photomicrograph of Spleen Showing Marked Deposition of Amyloid*

100 and the sodium to 136 milliequiv per liter, the carbon dioxide combining power was 22.3 millimols per liter, and the lactic acid was 2.8 mg and the phosphate 5.7 mg per 100 cc. The plasma reaction was pH 7.38.

During the next 2 weeks no desoxycorticosterone or testosterone was given, but Amigen and glucose were continued. Ankle edema appeared for the first time, and vomiting began. The nonprotein nitrogen rose to 116 mg per 100 cc, and the blood pressure fell to 84/44. Adrenocortical extract, desoxycorticosterone and testosterone were resumed. During the next 24 hours, however, the patient gradually became more and more dyspneic and began to have definite air hunger. It appeared to most observers that she was having tracheal obstruction at the site of the tracheotomy scar rather than dyspnea secondary to acidosis. Consequently, tracheotomy was repeated, with some transient relief. No definite obstruction was found at operation. The nonprotein nitrogen had risen to 143 mg per 100 cc, the chloride had fallen to 87, and the sodium to 130 milliequiv per liter, and the carbon dioxide to 13 millimols per liter. The blood pressure fell further to 70/30. The patient died 12 hours later.

**Autopsy.** Post-mortem examination was performed 14 hours later. The body was that of a well developed, thin Negress. Scattered areas of granulation tissue were present on about 2 per cent of the body surface. The most striking findings were in the spleen, liver, kidneys and adrenal glands.

The spleen weighed 240 gm. It was firm, and the cut surface was pale rose in color and dotted with pale, translucent areas about 1 mm in diameter. The architecture of the spleen was markedly altered. With the lowest magnification a section appeared to be composed almost completely of a homogenous red substance, with only scattered small zones of remaining splenic pulp. Under higher magnification, the red areas were seen to be malpighian corpuscles largely replaced by amyloid (Fig 1), a splenic artery being found with each area. This substance was arranged in irregular

masses and gave a positive reaction for amyloid when stained with Congo red.<sup>3</sup> Isolated cells and small groups of cells, consisting of lymphocytes and rarely red cells and polymorphonuclear leukocytes, lay between the masses of amyloid. The wall of the arterioles usually merged imperceptibly with the surrounding amyloid. In the areas of remaining splenic pulp, numerous red cells, a slightly increased number of polymorphonuclear leukocytes and macrophages containing golden yellow pigment were found. The walls of sinusoids and small arterioles and trabeculae were widened and appeared red and acellular, being composed principally of amyloid.

The liver weighed 1925 gm. The liver was congested and edematous and contained some amyloid. The degree of amyloidosis, however, was considerably less than that in the spleen and varied from section to section. Amyloid was found in the walls of small arterioles and larger arteries of the periportal areas. In widespread areas amyloid was found lying as large homogenous red masses between the sinusoidal lining and the hepatic cells. The hepatic cells were compressed in some areas. Amyloid was also found in the walls of large veins, lying just below the endothelium. The bile ducts were not involved. In areas not involved with amyloid the sinusoids were widened and filled with blood, and the liver cords compressed. Edema was suggested by the presence of a narrow space between Kupfer's lining and hepatic cells, pink granules were visible within this space in some places.



FIGURE 2 *Photomicrograph of Kidney, Showing Widespread Deposition of Amyloid*

The combined weight of the kidneys was 400 gm. The capsules stripped easily from a smooth surface. The cortices were mottled purple and yellow and measured 0.7 to 0.8 cm in thickness. They were poorly demarcated from the medullae, which were of a purple hue nearest the cortices and pale at the pyramids. There were six yellow stones measuring 2 to 3 mm in diameter within the left pelvis. In addition, there were small yellow granules of sand in the same pelvis. There were three similar stones in the right pelvis. The mucosa of the pelves and calyces were moderately injected. There was no exudate. The ureters and pelves were not dilated. The kidneys showed extensive amyloidosis. There was universal and marked amyloidosis of the glomeruli, interstitial vessels and tubules. The walls of the afferent vessels of the glomeruli were thickened and, for the most part, red and amorphous. Large masses of amyloid were present in the interstitial tissue and capillary walls of the glomerular tufts, resulting in narrowing and obliteration of the capillaries. The basement membrane of Bowman's capsule showed hyaline thickening. With few exceptions every artery or arteriole showed thickening of the walls with amyloid (Fig 2). In many vessels the lumen was obliterated. The veins were only occasionally and irregularly involved. There was amyloidosis of the tubules. This was not extensive and appeared for the most part in

the medulla. The amyloid was found in the region of the basement membrane of tubules. The tubules, however, showed striking changes in addition to the presence of amyloid. In many convoluted tubules some cells were swollen, pale and granular, whereas others were vacuolated and distended and appeared lace-like. The cells were often ruptured and the lumen of the tubules was often filled with pink cytoplasmic debris. No fat was demonstrable with sudan IV stain. Other convoluted tubules were widely distended and the epithelium was flattened. No mitotic figures were seen. A few of the convoluted tubules contained polymorphonuclear leukocytes and others contained masses of cellular debris. No hyaline casts were found. The interstitial tissue was congested. A few small foci of lymphocytes were present.

In the pancreas amyloid was found in the walls of the arterioles of the interstitial tissue. Arterioles of an occasional islet also contained amyloid. The islet and acinar tissue was unchanged.

The pituitary body was of normal size. Sections of the anterior lobe and pars nervosa showed amyloid within the walls of arterioles and in the walls of some veins. There was no apparent change in the cells of the anterior lobe.

The combined weight of the adrenal glands was 30 gm. The left cortex was of normal thickness and of a pale yellow color; the right was thin, shell-like and pale yellow. Both medullae were brown. The two adrenal glands were similar histologically. With lowest power the glands appeared to be almost totally replaced by homogenous, red-staining amyloid with the exception of a very narrow zone just beneath the capsule and the innermost cells of the reticularis and the medulla. The outermost cells of the zona glomerulosa were distinct and free of amyloid, and many contained fine vacuoles. These stained faintly with sudan IV. The remainder of the cortex except for a few clusters of cells of the zona reticularis contained considerable amyloid (Fig. 3). For the most part the cells and vessels were completely replaced by masses of amyloid. These were scattered short columns of cells where the cytoplasm blended with adjacent amyloid. Short double rows of cells occasionally separated and forming a tubule-like structure were found surrounded on all sides with amyloid. The cells of the medulla were relatively unaffected although the vessels contained amyloid in their walls. Formalin fixed frozen sections when examined with polarized light after warming and slight trauma showed only a rare doubly refractile body (cholesterol esters). Crushed cortex showed practically no refractile cholesterol esters. Little fat was demonstrable with sudan IV and when found appeared as small droplets within the cytoplasm of the narrow zone of unaffected zona glomerulosa lying beneath the capsule.

This patient with thermal burns developed in the twelfth month a syndrome characterized by profound and progressive weakness, decreased tolerance to barbiturates and general anesthesia, a low temperature, a low blood pressure, a rapid thready pulse, cold clammy extremities, convulsions and coma.

The diagnosis of Addison's disease in crisis was first made on clinical examination alone and was confirmed by the results of laboratory examination, which showed a marked lowering of the serum sodium, chloride and carbon dioxide combining power and an elevation of the nonprotein nitrogen. The diagnosis was further confirmed by the response to the hormonal and salt treatment, after which there was an immediate improvement in the clinical condition of the patient and a gradual return to normal of the sodium, chloride and carbon dioxide combining power and a fall in the nonprotein nitrogen.

Two weeks after specific treatment had been omitted the condition of the patient became worse, with dyspnea, weakness and a fall in the blood

pressure as the principal symptoms, and in spite of intensive hormonal treatment the patient died within twenty-four hours. Post-mortem examination disclosed generalized amyloidosis, with particular involvement of the adrenal glands and kidneys.

The abnormalities of the urine and the elevated nonprotein nitrogen can be explained by the extensive amyloidosis of the kidneys. It is also probable that renal failure contributed to the abnormal electrolyte pattern seen in the blood. The results of

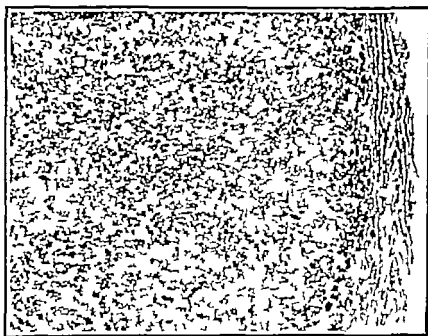


FIGURE 3 Photomicrograph of Adrenal Gland, Showing Marked Deposition of Amyloid in the Cortex Chiefly in the Zona Fasciculata

these electrolyte studies strongly suggest the retention of fixed acids in the blood. Renal failure, in certain cases, closely simulates Addison's disease.<sup>4</sup>

The insulin sensitivity and the decreased glucose tolerance observed on the first day were probably related to the transient disturbance of carbohydrate metabolism often seen following severe burns and other types of stress.<sup>5</sup> This is borne out by the fact that after the initial period of stress had subsided, the sensitivity to insulin and the glucose tolerance were normal. The sodium and chloride levels and the carbon dioxide combining power were normal on entry.

It is not possible to state categorically the etiology of amyloidosis in this case, which is the only one in which amyloidosis was observed in a series of 60 patients with burns examined at autopsy, many of whom lived several months but none over six months. In addition, a patient with extensive deep burns is still living, with the burns unhealed, after two years who to date shows no evidence of amyloidosis as judged by the Congo-red test. (This patient was discharged well on July 1, 1947, after three years in the hospital.)

It is probable that long-standing infection of the wounds was the chief etiologic factor. Several cultures revealed a hemolytic *Staph aureus* as the predominating organism, alpha-hemolytic streptococci, diphtheroids and *Pr vulgaris* also being present

in a majority of the cultures. It has been demonstrated that healing and skin grafting of extensive deep burns proceed more rapidly under conditions of adequate nutrition and that, in the presence of malnutrition, local exudation and presumably local infection of the granulating areas are increased.<sup>6</sup> This patient suffered from long periods of malnutrition during the course of her illness owing to the fact that it was possible to feed her adequately only when special nurses were available. At other times the amount of nursing care available was insufficient, largely because of the universal wartime shortage of nurses. The importance of special nursing care in inducing burned patients to take adequate diets and supplements has previously been emphasized.<sup>7</sup>

On the other hand, it is possible that the intermittent high-protein intake, consisting chiefly of milk, milk powder and Amigen, was a contributing etiologic factor, since feeding of cheese had been reported to cause amyloidosis in animal experiments.<sup>8,9</sup> At present, however, from the practical point of view, this possibility should be disregarded because of the marked importance of maintaining patients with extensive deep burns in good nutrition and the practical difficulty of administering sufficient

protein unless milk and derivatives of milk protein are freely used.

SUMMARY

A case of Addison's disease associated with amyloidosis of the adrenal glands that was part of a generalized amyloidosis following thermal burns is described. The Addisonian syndrome made its appearance a year after the initial injury.

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MEDICAL PROGRESS

WAR WOUNDS OF THE ABDOMEN

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A COMPLETE treatise covering all aspects of abdominal wounds observed in the United States Armed Forces in World War II probably will not be available for several years. On the other hand, many excellent articles on various phases of the problem have recently appeared. It seems worthwhile to collect and summarize the outstanding contributions that have been published before memories grow dim and interest flags. Obviously, no attempt can be made to include all papers. Nor can extensive considerations of tactical situations, closely related though they are to the care of the wounded, be included here.

The recent surgical care of the wounded differed radically from that in previous wars.<sup>†</sup> The extent of this change may be gauged by a brief summary of the therapy of abdominal wounds in the past. Interestingly enough, even in the early part of World War I all such wounds were treated con-

servatively just as they had been formerly.<sup>1</sup> Then a new era in surgery was inaugurated. It became apparent that nearly all patients with such wounds were sure to die unless operated on. Many of the wounded in World War I, however, were not admitted to a hospital for therapy as shown by the fact that of patients admitted to the hospitals only 11 per 1000 suffered from abdominal wounds. In the Fifth Army in the recent war 35 men per 1000 entered with abdominal wounds.<sup>2</sup>

It gradually became apparent that the time lag from wounding to surgical treatment must be reduced to the shortest possible interval if these patients were to survive. This was achieved in the Spanish War by the "three point forward system," described by Jolly,<sup>3</sup> who stated that abdominal wounds represent the best example of the type of case in which the time lag is supremely important for the saving of life. To achieve a reduction in the time lag, the casualty clearing station was divided into a casualty classification post, a hospital for the most urgent cases, including abdominal injuries,

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†Dr. Edward D. Churchill kindly contributed suggestions and information on the subject of initial surgery of battle wounds.

Find a second hospital for the less urgent. All three were separated, however, by ambulance transportation involving some delay between the triage center and the first hospital.

The British in the Libyan Campaign in World War II gradually evolved a method that was somewhat similar. The wounded were evacuated from the field dressing station by ambulance. As successive installations equipped for surgery were reached in the chain of evacuation, the most urgent cases were taken from the ambulances and retained for treatment. The selection was often cursory, however, and since the distance between the stations often required many hours of travel, many patients had to be evacuated too far.

The method employed by the United States Army was planned during the North African campaign and was first employed in the invasion of Sicily.<sup>4</sup> Thereafter, it was used throughout the war in the Mediterranean and European theaters. This procedure of triage undoubtedly contributed more to the saving of lives of the patients with abdominal wounds than any other single factor. The method was essentially as follows:

All casualties from the divisional area were collected at the clearing station, immediately adjacent to which a section of a field hospital was established. This institution was staffed by attached surgical teams composed of skillful surgeons, anesthetists, nurses and enlisted personnel with adequate equipment. Thus, even though the team was operating in the most unpleasant and often dangerous situations, the best care could be furnished the soldier at the time when operation was essential. Furthermore, resuscitation and surgery were amalgamated rather than dissociated as they had been in the past. Less urgent cases were sent immediately from the clearing stations to evacuation hospitals by ambulance. Likewise, patients from field hospitals were transferred to evacuation hospitals after initial surgery had been performed and convalescence well established. The dangers of early evacuation of these casualties had previously been shown by the British in the Middle East. Consequently, the field hospital was equipped to care for its patients in the early postoperative period.

Thus, during this war a new mode of treatment of abdominal casualties, based on the following considerations, evolved: the concept that abdominal injuries produce patients who are essentially non-transportable, surgery and early convalescence being transferred to the rear boundary of the division rather than the wounded being sent to the surgeon in the rear, the principle that resuscitation of patients with abdominal wounds must be rapid and effective, with the result that blood and plasma had to be instantly available in large amounts and surgery became an integral part in the process of resuscitation, the consideration that surgery must be radical and the benefits denied to none, and the concept

that proper anesthesia is of the utmost importance if the patient is to survive — the anesthetist is no longer an "ethnizer" but must be prepared to cope with all hazards of all types of anesthetics and to play an important part in the resuscitation of the wounded, as well as in the prevention of post-operative pulmonary complications.

New technical details that are of major importance in the management of abdominal wounds also

TABLE 1 Over-All Mortality following Visceral Wounds

SITE OF WOUND	MORTALITY IN AMERICAN EXPEDITIONARY FORCE (1917-1918)	MORTALITY IN BRITISH 8TH ARMY (1942)	MORTALITY IN SECOND AUXILIARY SURGICAL GROUP (1943-1945)	WOUNDS OF SINGLE VISCUS
	ALL CASES	ALL CASES	ALL CASES	%
Colon	60	59	37	23
Jejunum	70-75	53	30	14
Liver	66	49	27	10
Stomach	55	20	40	28
Kidney	23-30	65	35	16
Spleen	63	35	24	12
Rectum	45	52	30	14
Urinary bladder	50*	50	30	0
Duodenum	80	—	56	50
Pancreas	—	—	58	100
Gall bladder	—	20	30	0
Ureter	—	—	41	0

\*Approximate

evolved in World War II. The most important are as follows:

The exteriorization of wounds of the colon. Although this maneuver was employed in large ragged wounds of the colon in World War I, its value was not established until World War II. Kirk<sup>5</sup> described it as one of the important surgical advances in this war.

The evolution of an effective method of treatment of rectal wounds. The "retropentoneal syndrome," with death from extensive infection, was practically eliminated by wide local drainage and colostomy.

The thoracic approach for thoracoabdominal wounds. Dependent on advances in anesthesia, this technic has been almost wholly the product of World War II.

The elimination of enterostomy as a method of treatment of wounds of the small intestine.

The advances are reflected in various statistics that have appeared. Thus, the over-all mortality of patients with abdominal wounds admitted to American Expeditionary Force hospitals in World War I was 66.8 per cent.<sup>6</sup> The mortality of 381 such cases treated in the British Eighth Army during a three-month period in 1942 was 42.5 per cent.<sup>7</sup> In 2918 abdominal cases that had visceral wounds operated on by the Second Auxiliary Surgical Group in World War II the mortality was 25.5 per cent.<sup>8</sup> These figures do not adequately measure the actual improvement, for in World War I, only less severe wounds were operated on and fewer patients reached

the hospital. Thus, the mortality rate of the Second Auxiliary Surgical Group patients of a character comparable with those of World War I was about 13 per cent. On the other hand, the over-all mortality for all the armed forces will not be so low as that of the Second Auxiliary Surgical Group.

A comparison of the over-all mortality of the wounds of the various viscera in the American Expeditionary Force<sup>1</sup> in World War I and in the British Eighth Army (Libyan Campaign)<sup>7</sup> and the Second Auxiliary Surgical Group<sup>2</sup> in World War II is presented in Table 1. It will be noted that, because of the high incidence of wounds of multiple viscera, the over-all patient mortality is much less than that when the viscera are considered separately.

Several methods have been proposed to estimate the prognosis of the wounded. The most important are the time lag, the depth of shock on arrival in the field hospital and the multiplicity factor. These procedures require further consideration.

The time lag has been investigated by many surgeons, in an attempt to prove the obvious truth that delay in treatment increases the death rate. The variability of war wounds, however, introduces factors that make most such studies worthless. Thus, Brott and Childs<sup>2</sup> found that, if all cases are considered, "the mortality of any unselected groups of abdominal cases at any selected time interval from wounding to surgery is approximately constant." Ogilvie<sup>7</sup> even observed that an increased time lag works both ways, but chiefly toward a lower operative death rate and that delay causes peritonitis but also eliminates the worst cases. Consequently, Brott and Childs studied the mortality when the two variables—the time lag and the number of abdominal organs involved—were separated. These figures show clearly that the death rate rises with delayed treatment. Giddings and McDaniel,<sup>2</sup> studying a series of 355 cases in which the small bowel was the only viscus injured, found the mortality to be 7 per cent if the operation was done within eight hours, 14 per cent in twelve hours, 22 per cent in twenty-four hours and 30 per cent in forty-eight hours.

The depth of shock is difficult to estimate. Among the important considerations are the level of the blood pressure, the rapidity of the pulse, the pulse pressure, the state of the peripheral circulation as evidenced by cold, pale or cyanotic extremities and signs of cerebral anoxia. Of these features the most reliable, according to Towery,<sup>2</sup> are the trends of the blood pressure and pulse as resuscitative therapy is carried out. Beecher<sup>8</sup> noted that the pulse rate and the amount of sweating are of no value in estimating the depth of shock, on the other hand, the fullness of the pulse and the blood pressure level are of great importance. Since the blood pressure is the most reliable objective criterion of these features, the degree of shock has usually been measured by the level of the systolic pressure.

Towery and Welch<sup>2</sup> grouped their patients of Second Auxiliary Surgical Group in four categories. The degree of shock was said to be profound if systolic blood pressure on admission was 40 or below, severe from 41 to 70, moderate from 71 to 100 and incipient or no shock from 101 to 140. The mortality in these four groups was respectively 66.4 per cent, 50.4 per cent, 38.0 per cent and 18.1 per cent. These data show clearly that the prognosis may be estimated with some accuracy at the time the patient arrives in the field hospital.

The "multiplicity factor" has been shown to be of extreme importance in the determination of prognosis. This factor, as defined by Wolff, Chaffin and Giddings,<sup>2</sup> refers solely to the number of abdominal organs injured in a given case as determined at operation. In 2918 cases of abdominal wounds the mortality was 12 per cent if one organ was involved, 27 per cent with two, 46 per cent with three, 60 per cent with four and 88 per cent with five organs involved.

The nature of wounds of the abdomen caused by high-velocity shells has been investigated by Puckett, McElroy and Harvey.<sup>9</sup> Their studies show that the abdomen expands with the penetration of a high-velocity missile. This expansion persists for 1 or 2 milliseconds, and is followed by a constriction that lasts for 4 or 5 milliseconds and is succeeded by a second bulging of the abdominal walls of greater duration but less intensity. Coincident with the initial abdominal expansion there is a large temporary cavity within the abdomen. Internal damage to the viscera is far out of proportion to the wounds of exit and entrance. The general effect is that of an explosion within the abdomen.

The care of the wounded may be classified according to Churchill,<sup>10</sup> into initial, reparative and reconstructive phases. In terms of Army instructions of World War II, this means essentially care furnished first by the field and evacuation hospitals, secondly by the overseas general hospitals and finally by the general hospitals in the Zone of the Interior. Further discussion of abdominal wounds is divided into these three categories.

#### INITIAL SURGERY

Abdominal casualties must be evacuated rapidly as possible to a surgical unit prepared to handle them. Only primary measures of resuscitation, such as plasma administration and the temporary control of hemorrhage from accompanying wounds of the extremities, are employed before the patient reaches a surgical installation.

As soon as the patient arrives in the field hospital resuscitation is begun, his clothes are removed, wounds are inspected, and he is placed on a cot or litter. Thereafter, a rapid estimate of his general condition is made, x-ray films are taken, the stomach is lavaged, the urine is examined, pain is alleviated.

chemotherapy is begun, and surgery is instituted. Several of these measures require special consideration.

Resuscitation in abdominal cases involves primarily the administration of blood.<sup>11</sup> Plasma is administered while cross-matching is carried out. Thereafter, if the patient is in shock, 1000 cc of blood should be given in fifteen to twenty minutes and continued at a slower rate. The average abdominal case requires 1500 to 2000 cc.

The maximum time devoted to preparation of patients should be one and a half to two hours. If at that time there has been no response to treatment the usual causes of persistent shock must be considered. They are, according to Berry,<sup>12</sup> continuing hemorrhage, massive peritoneal contamination, pelvic cellulitis or clostridial myositis, a large evisceration, blast injury of the lungs, heart, abdomen or brain or other severe wounds.

Physical examination is directed especially toward a determination of the course of the missiles. All evidence points to the fact that they pursue straight courses through the abdomen. Any penetrating wound of the chest, back or thigh may represent a possible abdominal penetration. According to Stewart,<sup>13</sup> the most important errors in the pre-operative physical examination are failure to examine the rectum and omission of an examination of the peripheral nerves. If the possibility of a rectal wound exists and no blood is found on the examining finger, a proctoscopy must be done.

Auscultation of the abdomen is of value. Jarvis<sup>14</sup> found peristalsis to be uniformly absent with intraperitoneal perforation of a hollow viscus. On the other hand, absence of peristalsis is not diagnostic of perforation. Blackburn and Rob<sup>15</sup> observed peristalsis in the presence of lesions of the hollow viscera in only 5 of 89 cases, whereas in the absence of hollow visceral lesions, peristalsis was present in 64 cases and absent in only 1. Estcourt<sup>16</sup> noted active peristalsis in several patients who at operation were found to have perforation of the colon.

The primary purpose of x-ray examination is to determine the location of retained fragments and thereby to visualize the path the missile has taken.

The stomach tube, preferably one of large caliber, is passed, and the stomach emptied. It is a fortunate event when vomiting is induced by this maneuver.<sup>17</sup> Thereafter, a Levin tube is introduced and maintained during and after operation. Beech and Wolff<sup>17</sup> demonstrated that, with few exceptions, this procedure should be an integral part of the preoperative resuscitative program, regardless of the site of the wound.

If the patient cannot void, a catheter must be passed and the urine examined. If bloody urine is obtained it is better to avoid irrigation of the catheter until the abdomen is opened (Michels<sup>18</sup>).

Pain is more frequent after abdominal wounds than any other type.<sup>18</sup> Consequently, many patients

have been oversedated and during the progression of resuscitation have developed acute morphinism. Therefore, it is better to administer morphine by the intravenous route and in comparatively small doses.

Chemotherapy, which is instituted as soon as the patient arrives, usually consists of the intramuscular administration of 25,000 units of penicillin although, when available, up to 100,000 units has been given intravenously. The whole problem of chemotherapy is considered below.

When the patient is ready for surgery or when surgery becomes mandatory because his condition fails to improve, the anesthetic is begun. This should preferably be ether oxygen administered by a closed system through an intratracheal tube. To avoid the deeper levels of anesthesia, local or regional nerve blocks may be added. This is especially true in the upper abdomen, where the intercostal nerves may be blocked. Spinal anesthesia is contraindicated because of the deleterious effect on blood pressure. Pentothal sodium should not be employed as the primary anesthetic agent if there is any likelihood of abdominal penetration, since a long operation with adequate relaxation may be necessary.

The incision should give adequate exposure of the wounded section of the abdomen and should permit secure closure. Thus, if a colostomy may be necessary, the primary incision should be placed well away from the projected site of the stoma. Vertical paramedian incisions are usually preferable. In the upper abdomen, transverse or subcostal incisions may be used. Incisions through the wounds of entrance or exit, and transverse lower abdominal incisions should be avoided.

Ogilvie<sup>7</sup> states that "in the abdominal surgery of warfare technique may be summed up as a simple plan, a purposeful over-haul, and a rapid repair." Usually, on opening of the peritoneal cavity, blood, fecal matter or a mixture of both is encountered. The cavity is emptied of its fluid contents as rapidly as possible. If hemorrhage continues, usually the spleen, liver or large intra-abdominal veins have been wounded. Primarily, bleeding is controlled. Wounds of the abdominal wall should be carefully inspected, since they may furnish the site of the hemorrhage. Thereafter, the source of fecal contamination is determined. The colon is examined first, and any wound carefully walled off. The small bowel and stomach are observed in that order, and, finally the other viscera. When the entire damage has been ascertained, the various wounds are repaired.

#### *Visceral Wounds*

The incidence of involvement by organs in 2918 patients with visceral wounds received by the Second Auxiliary Surgical Group was as follows: stomach, 13.2 per cent, duodenum, 3.7 per cent,

jejunum and ileum, 37.0 per cent, colon and intraperitoneal rectum, 35.0 per cent, extraperitoneal rectum, 4.9 per cent, liver, 26.7 per cent, gall bladder and bile duct, 1.7 per cent, spleen, 10.8 per cent, kidney, 13.4 per cent, ureter, 0.8 per cent; urinary bladder, 4.9 per cent, pancreas, 1.9 per cent, and major abdominal vascular injury, 2.4 per cent.<sup>2</sup> The over-all mortality rate in this series was 25.5 per cent, varying from 26.6 per cent in winter to 19.7 per cent in summer. It was found that children and the aged wounded civilians withstood operative procedures poorly. Of the deaths, 48 per cent occurred on the day of operation, and 62 per cent within seventy-two hours. The causes of death were listed as shock (62.4 per cent), pulmonary complications (12.8 per cent), peritonitis (12.0 per cent), anuria (4.6 per cent), anaerobic infection (1.6 per cent), miscellaneous (4.0 per cent) and unknown (2.5 per cent).

Wounds of the following viscera are briefly considered.

**Stomach** Wounds of the stomach may be suspected preoperatively if blood has been vomited or aspirated through the nasal tube. The course of the missile in the series of the Second Auxiliary Surgical Group was thoracoabdominal in 47 per cent of cases, and abdominal alone in 53 per cent. Bolman and Caul<sup>19</sup> point out that the perforation may be entirely intrapleural, so that abdominal signs are entirely absent. It is clear that unless every possible penetrating wound of the diaphragm is explored, many of these wounds will be overlooked. The perforation of the stomach is often difficult to locate, especially if the abdominal approach is necessary and the laceration is high on the greater curvature. It is well to remember, as in all other wounds of the gastrointestinal tract, that unless the foreign body is found within the lumen of the viscus, there must be an even number of perforations, barring tangential lacerations.

Closure of the stomach should be by a careful two-layer suture. Purse-string sutures should be avoided, since secondary hemorrhage is more frequent from the stomach — because of its extraordinary vascularity — than from any other part of the gastrointestinal tract. No data can be offered concerning the merit of absorbable or nonabsorbable sutures in any part of the gastrointestinal tract. Many surgeons had more confidence in an outer layer of cotton or silk because of the established peritonitis present in most of the cases. Other surgeons used catgut throughout.

**Duodenum** In the great majority of wounds of the duodenum, the wound of entrance is in the right upper quadrant or in the back, posterior to the duodenum. The mortality is high because other viscera are frequently damaged. Accurate exposure of the retroperitoneal duodenum requires mobilization of the hepatic flexure of the right colon and section of the lateral attachments of the duo-

denum. In this manner the entire organ may be inspected. Repair is effected either by a two-layer closure or by resection and anastomosis.

If the patient survives the first few postoperative days, a fistula will form unless the closure has been satisfactory. In 20 cases in which transections were observed in the Second Auxiliary Surgical Group, only 6 patients lived through the sixth postoperative day, and fistulas developed in 2.

**Jejunum and Ileum** The small intestine is wounded oftener than any other abdominal viscus. Perforations are usually multiple and, because the ileum is longer than the jejunum, are more frequent in the former. It is essential to inspect all wounds of the intestine before repair, since if a resection is necessary other wounds may be included in the excised segment. Repair is either by suture or by resection and anastomosis. A two-layer end-to-end anastomosis is usually the procedure of choice, if resection is to be done, since it can be made more rapidly than a side-to-side anastomosis. It must be made with care to avoid late obstruction at the anastomotic line.

The individual surgeon must decide which procedure is to be employed. The British have recommended resection only as a matter of last resort. It was used much more frequently in United States Army hospitals. The essentials are first that all traumatized areas must be repaired and secondly, that the remaining blood supply must be adequate. Thus, any segment of intestine from which the mesentery has been detached for 5 cm or more should be resected because gangrene and perforation will occur later if it is left in situ. One resection can frequently dispose of several lacerations and severely traumatized bowel, in my opinion, this is more satisfactory than leaving areas of questionable viability that may perforate at a later time. Severe damage to the mesentery will also require surgery. It is to be expected that the mortality after resection will be higher than that after suture, because more serious injuries are included. Thus, Giddings and McDaniel<sup>2</sup> found in 1117 cases that the mortality following suture was 23.3 per cent and that after resection, 37.3 per cent.

Under no circumstances is an enterostomy desirable, except as noted below in wounds of the cecum. The depletion from rapid loss of secretions of the upper intestine is formidable. Fortunately, recourse to enterostomy was rare in World War II.

An interesting postoperative complication was reported by Hawkes and Spencer.<sup>20</sup> Following a thoracoabdominal wound with perforation of the upper small intestine and colon, there was massive bleeding from the colostomy. A total of thirty-five transfusions was employed. Twenty-two days after the injury, exploration revealed hemorrhage from an artery at the site of the closure in the jejunum. Resection was followed by recovery.

*Colon* The treatment of wounds of the colon has provoked more discussions than that of injuries to any other viscus. From a mortality of about 60 per cent in World War I, the death rate has been nearly halved, particularly because of the widespread adoption of the principle of exteriorization. The method, however, varies depending on the section of colon that is wounded.

It is important, in a discussion of wounds of the colon, to differentiate clearly three types of surgical procedures. In the first group a perforation of the bowel is discovered, the loop is exteriorized, and the "colostomy" has already been made by the missile. In a second group, there is extensive soft-tissue damage to the buttocks or a wound of the low sigmoid, but a careful suture of the perforation of the colon is possible, in these cases the sigmoid is exteriorized, and a small incision is made for temporary decompression that may be converted into a defunctioning colostomy by complete transection should it be needed. In the third group extensive wounds of the lower bowel, bladder or pelvis require a true colostomy that will entirely defunction the distal segment.

There are certain essential features in any colostomy. It should be placed in a separate incision from that employed for the laparotomy. Usually, a small muscle-splitting incision can be made. Wounds of entrance or exit should be avoided unless they are small, because of the increased chance of sepsis or breakdown. Adequate mobilization is most significant. The forward surgeon should remember that postoperative abdominal distention will shorten the colostomy and invite retraction into the abdominal wall. Most of the complications referable to colostomies observed in the overseas general hospitals could have been avoided if a proper site had been chosen for the colostomy, and the bowel widely mobilized.<sup>21</sup>

Colostomies are either of the loop or of the spur type. Acrimonious discussion was often heard from the partisans of both types in the overseas hospitals. Later, some surgeons working in the general hospitals of the Zone of the Interior advised complete division of both limbs of all colostomies to avoid any spill-over of feces from the upper to the lower segment. To the impartial observer, it seems that all these procedures have their indications.

The whole problem has been ably discussed by Mason,<sup>22</sup> who divides these wounds into the following groups: perforation of the antimesenteric portion up to half the diameter of the segment, which is best treated by a simple, no-spur, loop colostomy; perforations of the mesenteric border and of the antimesenteric border larger than half the diameter, which should be treated by a double-barrel spur colostomy; severely torn segments and complete transections, which also require a double-barrel spur colostomy; injuries to the mesentery producing nonviable segments, which are treated in the same

way, a sixth group, which includes the first five groups but in the injury to the rectosigmoid just above the peritoneal floor, in which repair must be effected and a loop colostomy done proximal to the injury, a seventh group, which includes the first five groups occurring in the rectum between the pelvic peritoneum and anus and in which Mason advises a loop colostomy, and injuries of the right portion of the colon necessitating right colectomy or cecectomy, which are probably best treated by a spur ileocolostomy. In addition, Mason states that areas of questionable viability may be exteriorized. Any perforation in an exteriorized segment may be closed, occasionally, the suture will hold.

Disagreement with the above conclusions will occur chiefly in the seventh and eighth groups. The rectal wounds are considered below, but it is necessary to discuss injuries of the right portion of the colon more fully here.

Wounds of the antimesenteric margin of the ascending colon may be converted into tube cecostomies. Small perforations without contusion of the bowel may be closed primarily by experienced surgeons. A large rubber tube is employed and is withdrawn in four or five days. If there is a small posterior wound of the cecum as well, it may be closed by suture, it is always important to mobilize the whole ascending colon to disclose such perforations.

A more difficult problem arises when there has been extensive damage to the ileocecal area and this whole segment must be resected. There are several ways of handling the bowel. Primary ileocolic anastomosis has occasionally given brilliant results, but is not recommended as a routine procedure, since the peritonitis produced by wounds of the ascending colon is the most virulent from all colonic injuries. A spur-type ileocolostomy may be done, the stoma being brought out in a separate incision. The profuse ileal drainage will be difficult to handle, serious problems in wound healing arise, and even deficiency states may appear quickly. Many surgeons followed this technic to the end of the war, holding the patients in the forward hospital for early (three or four days) crushing of the spur. This difficulty may be obviated by a side-to-side ileocolostomy, either the distal ileum or the proximal colon, or both, being brought out for decompression. A final suggestion is an ileocolostomy with wide separation of the two limbs.

The experience of the Second Auxiliary Surgical Group is of interest in this regard. The conclusions of Chunn and Hauver<sup>23</sup> were as follows:

Wounds of the ascending colon presented a particularly difficult problem when it was necessary to resect the entire right colon and terminal ileum. Early in the war the most popular procedure was the resection and double-barrel ileocolostomy. This procedure was not satisfactory and carried a mortality rate of 64.7 per cent. Later on, resection and ileocolostomy anastomosis and either double mucous fistulae or single mucous fistula was advocated.



and was done with some improvement in the mortality rate. However, this mortality rate remained high at 51.7 per cent. Two patients with resection of a portion of the ascending colon had the proximal and distal ends exteriorized and both patients died.

If a loop colostomy is to be made, the loop may be supported by a glass or rubber tube. If a spur colostomy is made, the spur should be made 15 cm long, and it should project 5 cm above the skin. The spur should be formed by two catgut sutures along the antimesenteric margin. The bowel should be opened on the operating table if the perforation is distal to it. In other cases it may be advisable to leave the clamp on for twenty-four hours until the wound is well sealed off.

**Rectum.** Wounds of the rectum are characterized by difficulty of diagnosis, inaccessibility, frequent damage to other structures, and the hazard of retroperitoneal infection. Laufman<sup>23</sup> notes that the missile may enter anywhere from the costal margin to the lower thigh. Only 6 per cent of patients with buttock wounds in his series had rectal perforations. The patient usually escapes injury to the rectum unless the missile crosses or is lodged near the midline. Patients with unsuspected and untreated rectal wounds are likely to die of profound toxemia.

When a rectal wound is present or suspected, the posterior wound should be débrided before the laparotomy is done, unless active intra-abdominal hemorrhage demands initial laparotomy. This will require adequate exposure of the tract of the missile, as well as exposure of the rectum through an anococcygeal incision that must be deepened through the fascia propria of the rectum. The coccyx will frequently need to be moved to secure wide drainage. If so, because of the possibility of osteomyelitis of the lower sacrum, as noted by Colcock,<sup>24</sup> the bone should be cleanly removed and the sacrococcygeal cartilage excised. The rectal wound is exposed. Closure is advocated by Croce, Johnson and Wiper<sup>25</sup> and Mason,<sup>22</sup> even though the chances of failure are high. The wound is packed lightly.

Laparotomy is then performed. If the rectal wound is small and uncomplicated a sigmoid colostomy with separation of limbs is wise. If there is extensive damage to bony pelvis and bladder, the colostomy should be made in the transverse colon.

A rectal wound is often first diagnosed at laparotomy. A retroperitoneal hematoma arising from the pelvis usually indicates damage to the rectum, and a colostomy should be performed accordingly.

Morgan<sup>26</sup> lists some of the complications that have been observed — namely, osteomyelitis, meningitis following removal of a shell fragment near the sacral canal, diphtheritic infection and secondary hemorrhage.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 33311

#### PRESENTATION OF CASE

A twenty-four-year-old man was admitted to the hospital because of pain in the back.

Two weeks prior to admission the patient noted a steady dull aching pain in the right flank, lasting about five or six hours and then subsiding. Four days later it recurred in the left flank, and subsequently he was never free from pain in either the right or left flank. The pain radiated to the front of the abdomen, was sometimes made worse by deep breathing, caused anorexia and at times prevented sleep. He had taken fluids without vomiting. He had noted an evening rise in temperature since the onset of the pain. On the day of admission he hiccuped continuously.

Since the age of eight the patient had noted increasing muscular weakness. Early there was a contracture of the toes, so that walking was possible only on the toes. Because of increasing weakness of the legs walking had been impossible for the past eight years, and by the time of admission the trunk and upper extremities were so weak that the patient could not lift his arms to shoulder level and could not arise in bed without aid. One year before entry he had suffered from palpitation, breathlessness and swelling of the legs. His physician told him that he had high blood pressure and gave him digitalis, which afforded considerable relief.

His parents were living and well but one brother out of five siblings and a maternal cousin suffered from similar muscular weakness.

The patient appeared too acutely ill to permit extensive examination. He was obese, and the muscles were generally weak, although they appeared and felt hypertrophied, especially the calf muscles and biceps. The lower extremities were cold, livid and pulseless. The fundi were poorly visualized but revealed narrowed arterioles. The throat was slightly injected. The chest was clear. A forceful apex impulse was felt 3 cm. beyond the midclavicular line, and a Grade I systolic murmur was audible at the apex. The pulmonary second sound was considerably louder than the aortic. The abdomen was distended and tympanitic, with diminished peristalsis. There was tenderness in the right costo-

vertebral angle and right flank and to a less extent in the left costovertebral angle. There was extreme weakness of all extremities, with equinus deformities of the feet and hypertrophy of the calf tissues.

The white-cell count was 15,800, with 92 per cent neutrophils, the red cell count was 5,100,000, with 15 gm. of hemoglobin. The urine on two occasions gave a ++++ test for albumin, and the sediment showed occasional hyaline and granular casts and, on one examination, 30 to 40 white cells and 2 to 3 red cells per high-power field. X-ray films revealed enlargement of the heart, particularly in the region of the left ventricle. The cardiac apex lay within a fingerbreadth of the chest wall. There was questionable notching of the ribs. The aorta could not be traced. The lungs were clear. There was an area of translucency between double contours of the right leaf of the diaphragm.

The temperature rose from normal on admission to 103°F. in the afternoon and fell to normal again by the following morning. The pulse was around 120, and the respirations about 20. The blood pressure was 110 systolic, undetermined diastolic.

Hiccups continued the day after admission, and the patient complained of some shortness of breath. The nonprotein nitrogen was 54 mg. per 100 cc. Later that day he was found to be breathing in Cheyne-Stokes rhythm, the neck veins were distended, and the pulse was 120, with an audible gallop. He was cold and sweaty, and the blood pressure was not obtainable. The chest was clear to percussion and auscultation. Later in the morning he improved, the blood pressure was 90 systolic, 70 diastolic, and the pulse was still 120, and the breathing was regular. An electrocardiogram was not remarkable, except for evidence of some degree of bundle-branch block. By evening the respiratory difficulty had again developed, without evidence of fluid in the chest. He expired at 1:00 the following morning, forty-eight hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. MARIAN ROPES. To me this picture is extremely confusing. Many systems are involved, and it is difficult to find the interrelation between the diseases. The predominant involvement is in the neuromuscular, cardiovascular and renal systems, with possible or probable gastrointestinal-tract involvement. The neuromuscular involvement was of sixteen years' duration and consisted of progressive muscular weakness. There are various causes of such a condition that one must think of. Myasthenia gravis is the first, for which I find little evidence. There is no evidence for dermatomyositis. I think that the likeliest explanation for such a steady progressive muscular weakness with some disproportion in the size of muscles is myopathy—muscular dystrophy. If this is the cause of the muscle disease, there is no evidence that it is related to the terminal illness, which began two weeks before death. It

would be intriguing to try to link them together, but the only possible way that I can is by some involvement of the vascular system, presumably an anomaly of some kind. On admission the legs were cold and pulsations could not be felt. There was also questionable notching of the ribs. It seems probable to me that the majority of the changes in the legs were of acute onset and related to the terminal illness. Whether or not he had any alteration of blood supply to the lower extremities before the last two weeks is difficult to say. Perhaps at this time the x-ray films would help us out, especially in regard to the questionable notching.

DR STANLEY M. WYMAN: The films could not be found for demonstration here, but I remember that we argued about them at some length. It was the majority opinion that they were not true notches, since they all occurred at the same area in the rib.

DR ROPES: That is disturbing because there are two differential points that I had hoped the x-ray films could help us with. One was the question of notching. If notching was present, coarctation should be seriously considered.

The second question is whether or not the area of translucency was definite enough to conclude that there was air under the diaphragm. Apparently we are not going to have the opportunity to look at the films to see if it was impressive enough to include rupture of a viscus as one of the possibilities.

To return to my attempt to see if in any way the neuromuscular disease can be linked to the terminal illness, vascular anomaly has to be considered. Coarctation alone would not, to my mind, explain the weakness involving the upper extremities. Progressive weakness and atrophy of all extremities can occur with hypoplasia of the aorta. This may be found with a large or small heart, and it is usually associated with accentuation of the pulmonic second sound, which was present here. The course of such a condition, however, is slowly progressive congestive failure. I see no evidence of such progressive congestive failure in this case. I doubt that hypoplasia of the aorta could explain all this picture and therefore it is not a way of linking the neuromuscular disease to the terminal disease.

To turn to the final illness of two weeks' duration, I find three possibilities that have to be seriously considered. The first is rupture of a viscus, which I have mentioned. The seriousness with which we consider this depends to some extent on whether or not there was air under the diaphragm. If rupture occurred I doubt that it happened at the time of onset of symptoms two weeks before admission. It is much likelier that infarction occurred at that time and then eventually, rupture. I should expect, however, more evidence of peritoneal irritation at some time during the course than is apparent here. The terminal episode would presumably have to be explained by some secondary event, such as pulmonary embolism.

Another group of events, which I considered as one of the possible explanations, is embolism, pulmonary or renal, or both. There is little definite evidence for pulmonary embolism anywhere in the story. The increased pulmonary tension is suggestive evidence, but surely not more than that. The location of the pain — in the flanks and abdomen — is unusual for that associated with pulmonary emboli. Again if one considered that pulmonary emboli occurred in this patient and were the cause of the terminal episode, one would have to introduce other factors to explain certain findings, such as the renal disease. That could have been caused by pre-existing renal disease or by emboli to the kidneys with infarction. There is absolutely nothing in the history to indicate the former unless one considers the slight suggestion of arterial narrowing as suggestive. The pain is surely consistent with the latter diagnosis, but the location is utterly consistent. In regard to the source of such emboli in the systemic circulation, I find it necessary to introduce the possibility of infection, either on an abnormal aortic valve, for which there is little evidence, or coarctation, if such exists. The laboratory evidence in this case is of little help in differentiation. We have evidence of leukocytosis, with a polymorphonuclear reaction and fever. If one considered renal emboli as the initial episode one would have to introduce something else to explain the cause of death — such as a pulmonary embolus or disease in the aorta.

The third possibility is a dissecting process in the aorta. If this were present, one would see it in a patient of this age only in the presence of some vascular anomaly. It could occur in a person with coarctation of the aorta, in which case the final dissection and rupture could reach the pericardium and cause pericardial tamponade. In this respect it would be helpful to know that there really had been a sudden cardiac enlargement. That is something we cannot know, however. The final picture, I think, is consistent with bleeding into the pericardium.

In reconsidering the total picture, I find it difficult to differentiate these three groups of possibilities, for which there is little evidence. So far as I am concerned it is a choice between three types of possibilities, no one of which satisfactorily explains all aspects of the picture. I neglected to say that, had dissection occurred from coarctation of the aorta, it is conceivable that increased obstruction to flow could have caused decreased blood supply to the legs and kidneys with infarction explaining the renal findings. So if I still must choose between these three groups in the absence of being able to determine which is the likelier, I will place first the uncommon possibility, namely, coarctation of the aorta, with subsequent dissection and rupture. The possibility of superimposed infection cannot be ruled out. I think the best explanation of the

neuromuscular findings is muscular dystrophy, although it is intriguing to attempt to conceive that this whole process was related to generalized vascular disease or possibly to a vascular anomaly

DR WALTER BAUER How tall was this man? How much did he weigh?

DR TRACY B MALLORY He weighed 210 pounds. He looked like a powerful man, around 6 feet tall

DR ROPES I was thinking of a small person, I must admit.

DR BAUER How many white-cell counts were done?

DR MALLORY Only one is recorded

DR BAUER Were there any eosinophils in the smear?

DR MALLORY No

DR TAYLOR, do you want to give us the impression on the ward?

DR ISAAC TAYLOR I saw the patient in the Emergency Ward. He presented the picture of shock and severe pain in the back, in addition to what appeared to us to be muscular dystrophy

DR BAUER Where in the back?

DR TAYLOR In the right costovertebral angle radiating around the right flank toward the inguinal region

At that time he gave a history of having been in congestive failure one year previously, and in response to pointed questioning he said that the doctor had told him that he had high blood pressure. He was placed on digitalis and maintained a normal pressure until shortly before admission. The impression in the Emergency Ward was that he was suffering from congestive failure, which accounted for the low blood pressure in the face of a history of high blood pressure. The x-ray films of the lungs were clear, showing no evidence of congestion

DR BAUER What were the signs of congestive failure?

DR TAYLOR Cyanosis and respiratory distress. The enlargement of the heart on x-ray examination was quite marked, with a prominent left ventricle

DR BAUER Did the pain radiate anywhere other than to the anterior abdominal wall? Did it go to the legs?

DR TAYLOR No. It radiated from the right costovertebral angle around the right flank to the inguinal region. It did not go into the testicles or legs

DR BAUER Were the heart sounds distant or faint? Was there a gallop rhythm?

DR TAYLOR The heart sounds were of good quality. I heard no gallop

DR MALLORY Dr Ropes, do you care to say anything more?

DR ROPES I think not

DR BAUER I am tempted to suggest another possibility on the basis of the white-cell count, which was 15,000, with 92 per cent neutrophils, and a temperature of only 101°F. The count seems

out of proportion to the degree of fever. In bizarre cases such as this, these findings should always cause one to entertain the possibility of periarteritis nodosa. I believe that periarteritis nodosa with an aneurysm or two could explain everything this man had. On first reading the case, I wondered about congenital hypoplasia of the vascular system. This man's size and weight are against that diagnosis, however. I take it that he had pseudohypertrophic muscular dystrophy, particularly with the family history. Just to throw in another red herring, I shall say that the diagnosis was periarteritis nodosa, with a few mycotic aneurysms, one of which may have ruptured

#### CLINICAL DIAGNOSES

Progressive pseudohypertrophic muscular dystrophy

Coarctation of aorta

Glomerulonephritis?

#### DR ROPES'S DIAGNOSES

Muscular dystrophy

Coarctation of aorta, with dissection and rupture into pericardium

Renal infarction?

#### ANATOMICAL DIAGNOSES

*Pseudohypertrophic muscular dystrophy*

*Fibrosis of myocardium*

Cardiac hypertrophy and dilatation

Mural thrombi, left ventricle

Infarcts of spleen and kidneys

#### PATHOLOGICAL DISCUSSION

DR MALLORY Although this was the type of case in which we should have liked to do everything, the post-mortem examination was limited to an abdominal incision. I believe that we have most of the answers, however. The heart was greatly hypertrophied, weighing 600 gm. There was no coarctation of the aorta, but the aorta was extremely small, measuring only 4.5 cm in circumference. The lungs were congested and showed no infarcts. There were no pulmonary emboli. The cause of the flank pain was quite obvious when we looked at the kidneys. The right kidney was totally infarcted, apparently in two stages, since the upper pole was yellow whereas the lower one was grayish red. The right renal artery was completely occluded by a thrombus. The left kidney, which was larger than the right, showed a single large infarct. The left renal artery was patent. The liver showed marked chronic passive congestion, with necrosis of the cells in the central half to two thirds of the lobules. The spleen was enlarged, firm and congested and weighed 400 gm. We believe that there was adequate anatomic evidence for a diagnosis of cardiac failure. Whether the immediate mechanism of death was renal, cardiac or peripheral circulatory failure is impossible to decide on anatomic grounds.

The skeletal muscles showed almost complete replacement with fat tissue in many areas, in other fields the muscle fibers persisted but were most

patches of fibrosis throughout the myocardium, and the muscle cells themselves showed fresh patches of acute degeneration. Also there was con-



FIGURE 1

abnormal. Some were hypertrophied, and others extremely atrophic (Fig 1). There were foci of

siderable infiltration of fat tissue, not uncommon in elderly people but most unusual in a man twenty-

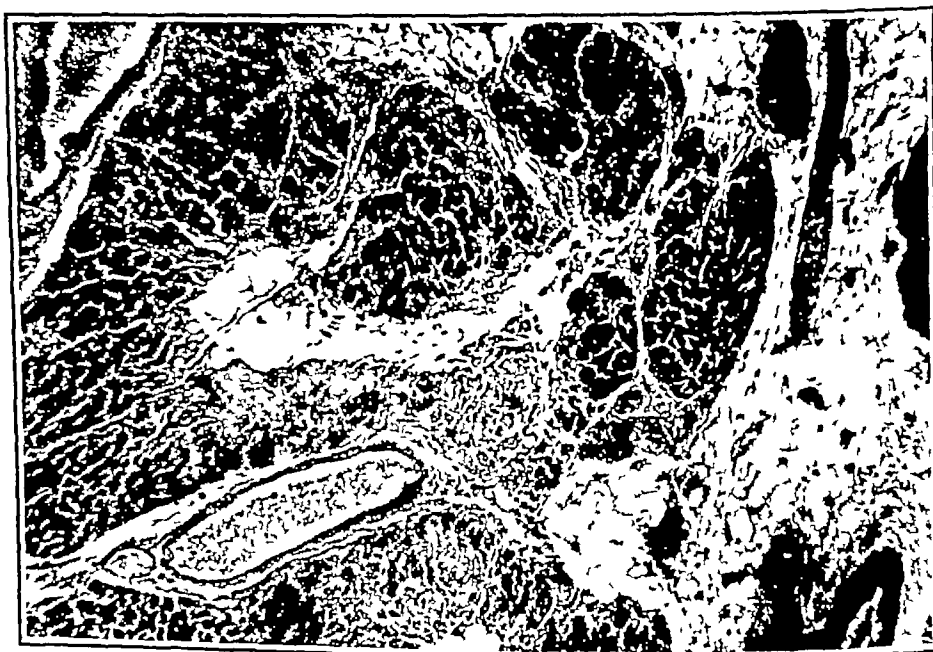


FIGURE 2

fibrosis. The picture was typical of pseudohypertrophic muscular dystrophy.

There have been a number of reports of severe sclerosis of the myocardium in patients with muscular dystrophy. The heart showed extensive

four years old (Fig 2). I believe that we have the right to assume that this myocardial change is part and parcel of the muscular disease.

DR. EDWARD F. BLAND: Did he have mural thrombi?

DR MALLORY Yes, on the wall of the left ventricle lying between the columnae carneae They were evidently the source of the emboli

DR BAUER Did he have auricular fibrillation on entry?

DR MALLORY I think that the rhythm was normal The thrombi here were ventricular rather than auricular, as they would be in auricular fibrillation

DR BAUER Was there any vascular disease?

DR MALLORY No

DR BAUER Can you tell us more about this type of heart?

DR MALLORY So far as I can recall, it is the only one that we have seen

DR BAUER Tell us what others have seen

DR MALLORY Globus<sup>1</sup> was the first person to report this condition carefully, as far back as 1918 Since that time various single cases have been reported, and Bevans<sup>2</sup> recently reported a pair of cases, with extensive atrophy in the myocardium and with fibrosis and with fatty infiltration, corresponding exactly to what was seen here These changes are sometimes visible in gross, sometimes microscopically

DR BAUER Do these patients have hypertension?

DR MALLORY I do not know

DR BAUER I followed a fairly large group of cases of muscular dystrophy with Dr Aub at the time when they were being treated with adreno-cortical extract A few of these patients are still being seen, but I never happened to see one with this type of heart disease Have you any idea how often it occurs—in 1 per cent, 20 per cent or 50 per cent?

DR MALLORY I have seen no figures

DR BAUER It must be reasonably rare, because some of the people we followed are now well over forty years of age

DR MALLORY Dr Walter Timme, in the discussion of Dr Globus's paper, stated that this was commoner in people with acute progressive disease and who died relatively early in life than in those with the slowly progressive type, he did not give any figures, however

DR BLAND Were electrocardiograms made in your cases, Dr Bauer? The electrocardiogram on the case we are discussing showed no abnormality, except bundle-branch block, which is misleading

DR MALLORY There has been a note in several cases that the electrocardiographic changes were slight or entirely absent

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#### CASE 33312

#### PRESENTATION OF CASE

A sixty-five-year-old unmarried woman entered the hospital complaining of abdominal cramps

For one year the patient had noted that she tired easily Three weeks before entry to the hospital she had had some mild cramps in the lower abdomen Five days before admission the pain recurred, it became worse the next day and continued until she entered the hospital For forty-eight hours prior to entry, the crampy pain was constantly present For three days the patient had vomited repeatedly Nothing had been passed by rectum for four days The patient had not urinated for two days

The patient denied previous melena, diarrhea, constipation and genitourinary symptoms She did state that many years previously she had had some sort of abdominal pain, which was in the midlower abdomen and spontaneously disappeared She had had no abdominal operations

The patient appeared acutely ill The extremities were cold and clammy The heart and lungs were essentially normal The abdomen was protuberant, tense, exquisitely tender and tympanitic throughout A fluid wave was present Peristalsis was diminished No spasticity or masses were present Rectal examination revealed a small uterus and marked tenderness on motion of the uterus, no masses were felt

The temperature was 99°F, the pulse 140, and respirations 24 The blood pressure was 130 systolic, 70 diastolic

The white-cell count was 31,700, predominantly neutrophils X-ray films of the chest showed a normal heart There were linear areas of increased density at the left base An abdominal film showed no dilated loops There was free air beneath the right half of the diaphragm, which was high, and there was a suggestion of gas within the liver

An abdominal tap on the day of entry produced cloudy, yellow, odorless fluid containing many pus cells and numerous gram-negative bacilli and cocci on smear A transfusion was given, and gastric suction instituted The temperature rose to 102°F and the patient appeared to sink into circulatory collapse, she died on the morning after admission

#### DIFFERENTIAL DIAGNOSIS

DR GORDON A DONALDSON One might guess from the length, breadth and depth of this history, particularly the past history, that this patient had entered the Emergency Ward unaccompanied by anyone who might have aided her in giving an account of herself I got the impression on second reading that she was practically in extremis on admission and that diagnostic studies were strictly limited

It is quite obvious that she had an overwhelming peritonitis and was in shock therefrom—and even—

tually died of peripheral circulatory collapse. The single blood-pressure reading is in discord with such a picture but may represent a relative hypotension in this patient. The abdomen was protuberant and tense, compressing the lower lung fields. Although no spasm is reported, the abdomen was exquisitely tender, and the lack of reflex spasm was probably due to her serious general condition. In spite of the fact that a fluid wave was present, tympany also existed, and this, as well as the finding of air under the diaphragm, indicates the pressure of extraluminal gas. I am rather surprised that any peristalsis was heard. Certainly the lack of bowel function can be explained on the basis of widespread peritonitis, and I should like to explain the anuria on the basis of renal hypotension, secondary to the same process. In all probability, she had been in a state of relative shock forty-eight hours previous to hospital admission.

The few remarks about the past history are not helpful. The progressive fatigue could have been due to secondary anemia. "many years previously she had had some sort of abdominal pain, which was in the midlower abdomen and spontaneously disappeared." This may have been due to any process — from appendicitis to dysmenorrhea. Perhaps I am dismissing this episode too lightly. We do know positively that the bowel habits had been regular and that she had had no urinary symptoms. This forces the conclusion that the present episode was acute and fulminating.

It is important that the initial discomfort was cramp-like and later became steady. This to me usually indicates that the organ involved was capable of peristalsis against an obstruction and that eventually there was perforation or disintegration, with local spread of the process. A tubular or a solid structure, such as an ovary, may twist on its pedicle repeatedly and finally infarct, but it is unlikely that such a process could persist over a matter of three weeks. We can also say that the organ under question probably contained gas or gas-producing micro-organisms. It is unlikely that blood-borne, gas-producing organisms, nurtured in an infarcted solid organ, would give such a picture at the end of five days.

One other point of note is the position of the pain — always in the lower abdomen. The initial sympathetic reference was into the lower abdomen, as well as the later somatic pain. The large bowel or genitourinary organs become the likeliest source of her disease.

From the x-ray films I should like to know the status of gas in the bowel and just where in the liver the air existed.

DR STANLEY M. WYMAN: This upright film of the chest shows the free air beneath the right half of the diaphragm, which is higher than usual. There appears to be some linear atelectasis in the base of the left lung field. The heart is not remarkable.

The aorta is markedly tortuous, the proximal descending portion swings far to the right, and there is calcification in the wall.

This view, with the patient lying on her side, shows the gas beneath the diaphragm to move freely over the lateral surface of the liver. I am unable to see definite evidence of the suggested gas in the substance of the liver, but the liver is not well shown on the film of the abdomen. The free gas is seen lying high and medially. There is probably fluid in the abdomen, but no evidence of dilated loops of bowel. There is a lot of opaque material scattered throughout the abdomen, much of which may lie in the bowel. There is no mention of a previous barium examination or of the patient's taking medication. This appearance raises the question of calcification in an ovarian tumor, such as a papillary cystadenocarcinoma, although the shadows are unusually dense. This question cannot be answered unless we can exclude the possibility that the opaque material was in the bowel. I can see no evidence of unusual masses.

DR DONALDSON: Air in the liver deserves special comment. It can get there by two routes. The usual course is via the biliary tree, in a retrograde fashion. Less frequently the portal blood stream conveys gas-producing bacteria, which are nurtured in the liver.

What could this have been? I am going to rule out the ureters and bladder. The uterus was small. This does not exclude it from torsion, infarction or perforation of a pyometrium. The age and marital status are compatible with spontaneous rupture of a pyometrium, but the organisms found are usually of many types and the pus is foul-smelling rather than odorless.

Torsion of a salpinx or ovarian cyst with late rupture should always be considered in an elderly patient, but it seems unlikely that free gas would be present within the abdomen and that the peritoneal fluid would show on smear gram-negative bacilli and cocci.

Could she have had a pancreatitis with ascites to throw her into such a state of collapse? I should have expected the collapse to have occurred days previously.

Appendicitis in elderly people rarely causes a textbook history, and epigastric symptoms are often lacking, particularly if there have been previous attacks. Inflammation of a Meckel's diverticulum, with perforation, seems unlikely since the pain was always in the lower abdomen.

Could this patient have passed a gallstone three weeks previously, which was wafted down the small bowel with mild symptoms and eventually became lodged in the large bowel? She gives no history of biliary dysfunction, and usually these stones become stuck in the region of a Meckel's diverticulum or at the ileocecal valve. If they do not cause obstruction and perforation in the small bowel, they should

pass through the large intestine. On the other hand, a spontaneous cholecystojejunostomy fistula is the most usual route of entry of gas within the liver shadow.

Against the diagnosis of diverticulitis of the large intestine with perforation is the lack of previous history of bowel difficulties, particularly constipation. Usually there is a long story of poor bowel habits, and in 18 per cent of Dr. Smithwick's\* series there was a story of bleeding by rectum. The patient could have had leakage through a diverticulum with local abscess formation three weeks previously, and then, five days before admission, a fresh burst from the abscess, with the fatal result that so often follows a second peritoneal insult.

This patient probably had a tumor of the descending colon that had caused mild obstructive symptoms for three weeks and had finally ruptured. In disagreement with this diagnosis is the fact that there was no really dilated bowel by x-ray study. Three weeks of subacute intestinal obstruction should result in some degree of bowel dilatation, particularly in the presence of terminal peritonitis. Also, the pus obtained at tap was odorless. This bothers me considerably, although it is possible to obtain odorless pus from some cases of large-bowel perforation, such as when the appendix is involved. Certainly, perforation of such a tumor would result in free air within the peritoneal cavity, and by a pyelephlebitis, gas-producing organisms might have been carried to the liver.

#### CLINICAL DIAGNOSIS

Generalized peritonitis (cause unknown)

#### DR. DONALDSON'S DIAGNOSIS

Pleuritis, probably secondary to carcinoma of colon

#### ANATOMICAL DIAGNOSES

*Benign peptic ulcer of stomach, with perforation and mesenteric abscess*

\*Smithwick, R. H. Experiences with surgical management of diverticulitis of sigmoid. *Ann. Surg.* 115:969-985, 1942.

*Perforation of mesenteric abscess, with generalized peritonitis*

Congenital anomalies: right-sided aorta and anomalous origin of left subclavian artery

Arteriosclerosis

Leiomyomas of uterus

Carcinoids of ileum

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY. Dr. Donaldson was quite correct in predicting that the peritonitis in this case was due to a perforated viscus. He was also right in suggesting that the leakage occurred in two stages — first, local abscess formation and, later, rupture of the abscess with generalization of the peritonitis. He was completely wrong, however, in his localization of the process. Despite the fact that all the symptoms were lower abdominal, the primary lesion was in the stomach. We found a benign peptic ulcer high up on the posterior wall, only 7 cm. from the cardia, and close to the greater curvature. An abscess 7 cm. in diameter was present in the gastrocolic ligament that had a thick fibrous wall and was evidently of some weeks' duration. The abscess communicated through two small perforations with the lumen of the stomach through the base of the ulcer and with the general peritoneal cavity.

There were numerous incidental findings. The major arterial trunks were anomalous. The right common carotid and subclavian arteries arose separately from the aortic arch, the left subclavian artery was low and came off at the junction of the arch and descending aorta. The arch itself turned directly backward instead of crossing the vertebral column, and the descending aorta lay to the right of the trachea and of the vertebral column. Evidently there had been no cardiac embarrassment from this dextroposition, since the heart was of normal size.

The uterus contained several small fibroids and the ileum several carcinoid tumors, none of them large enough to have caused intestinal obstruction.



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## EXUDATIVE TONSILLITIS AND PHARYNGITIS OF UNKNOWN ETIOLOGY

THE Commission on Acute Respiratory Diseases is again calling attention to a group of acute upper-respiratory-tract infections of unknown origin that it is important to differentiate from streptococcal infections of the throat.\* In the course of studies on acute respiratory diseases carried out over a three-year period at Fort Bragg these workers encountered many cases of exudative tonsillitis and pharyngitis in which beta-hemolytic streptococci could not be incriminated as the causative agent. Indeed, it was quite conclusively demonstrated that about half the cases of tonsillitis and pharyngitis that they studied had neither bacteriologic nor serologic evidence of streptococcal infection.

\*Commission on Acute Respiratory Diseases. Exudative tonsillitis and pharyngitis of unknown cause. *J A M A* 133:588-593, 1947.

Clinically, a comparison of the cases of unknown cause with those that were proved to be of streptococcal origin revealed distinctive characteristics of these groups as a whole, but the clinical findings were of little help in the differential diagnosis of individual cases. In general, the streptococcal infections had a more acute onset than the cases of unknown etiology. In the latter, chilliness, feverishness, headache and malaise — symptoms indicating systemic reaction — were slightly less frequent. On the other hand, the nonstreptococcal infections tended to involve the lower respiratory tract, as evidenced by the greater incidence of hoarseness, productive cough and pain in the chest. Sore throat and dysphagia were encountered with about equal frequency in both types of cases.

Physical examination also revealed some features that were helpful in the differential diagnosis. The patients in the streptococcal group gave the appearance of a more serious illness, they often showed diffuse redness of the mucous membranes of the palate, tonsils and posterior pharyngeal wall, and in the majority of them some edema of these tissues was also evident. Enlarged and tender lymph nodes, in particular, were more frequent in the cases of streptococcal infection. When caused by the streptococcus the tonsillar or pharyngeal exudate was usually yellow and extensive. By contrast the exudate seen in the nonstreptococcal cases was white or gray, was often of pinhead size and was frequently distributed over enlarged follicles of lymphoid tissue on the posterior pharyngeal wall.

The white-cell counts were also of some value in the differential diagnosis. Leukocytosis was a feature chiefly of the streptococcal cases, in which the average total count was about 13,000 with 79 per cent neutrophils, as compared with an average of about 9,000, with 67 per cent neutrophils, in the nonstreptococcal cases. Although both diseases are of short duration, with fever generally lasting less than four days, the maximum temperature tended to be higher in the streptococcal cases than in those of unknown cause, the average was 102.5 in the former, and 101.7°F in the latter. Although the differential diagnosis between the streptococcal and nonstreptococcal cases can ordinarily be made on clinical grounds, on the basis of

the criteria mentioned, cultures or serologic methods must be employed for accurate diagnosis. It is particularly important to differentiate these forms because the nonstreptococcal infection is a benign disease without important complications, whereas the streptococcal infections may give rise to serious and crippling sequelae. Intelligent management of such cases, therefore, requires cultural and serologic confirmation of the diagnosis.

The finding of streptococci in throat cultures may not always be adequate to establish a diagnosis, since normal subjects and those with undifferentiated respiratory infections may harbor streptococci, without the production of antibodies. Throat cultures from such persons, however, usually reveal only small numbers of streptococci, whereas the cultures in the true streptococcal infections, in which an antibody response is elicited, frequently yield a predominant growth of hemolytic streptococci.

The cause of the type of exudative tonsillitis and pharyngitis that the Commission on Acute Respiratory Diseases described is unknown. No single bacterial agent could be incriminated, and it was presumed to be a disease of nonbacterial origin. On epidemiologic grounds, it was thought that these cases might represent a variant of "epidemic undifferentiated acute respiratory disease." The incidence of this form of infection in civilian practice is not known, but it has been encountered with varying frequency, particularly in areas where epidemics of streptococcal infections have not been frequent or extensive. The suggestion is advanced that, because of the generally mild character of the disease, its short duration and the freedom from complications, this condition should be sought for among patients treated at home rather than among those treated in hospitals.

#### NONTUBERCULOUS PULMONARY CALCIFICATION

The methods generally used in surveys designed to discover cases of tuberculosis in its early stages and those intended to determine the probable incidence of the disease in the community include roentgenograms of the chest and tuberculin tests. The occurrence of demonstrable lesions in x-ray films, particularly areas of calcification with en-

larged hilar nodes, has traditionally been considered to be evidence of tuberculous infection, and such lesions are usually accompanied by positive cutaneous reactions to tuberculin.

Recent surveys, particularly those in certain sections, such as Kansas City, Missouri, and Tennessee, have revealed a large number of persons with areas of calcification in their lungs and negative tuberculin tests.<sup>1-6</sup> Such a situation is ordinarily interpreted as evidence of anergy and is encountered in cases of miliary tuberculosis and sometimes during other active acute infections, notably measles. It is known, however, that certain other conditions, such as coccidioidomycosis in the active or end stage, may give similar roentgenographic findings, but the latter disease could not account for the findings in the recent studies.

Extensive studies in several areas among school children and student nurses have indicated a close correlation between the incidence of those who are tuberculin negative and x-ray positive and that of positive reactors to histoplasmin.<sup>1-7</sup> This is particularly close in persons with disseminated areas of calcification in the lungs. The findings suggest that histoplasmosis or some other disease that produces pulmonary lesions and results in sensitivity to histoplasmin is prevalent. Interestingly enough, the regions where the incidence of x-ray-positive, tuberculin-negative and histoplasmin-positive cases is the highest correspond to those from which proved cases of histoplasmosis have been reported. Among student nurses the area of highest incidence was found in the eastern central states, and the frequency of the occurrence of such cases diminished progressively in proportion to the distance from this area.<sup>8</sup>

The surveys that included histoplasmin skin tests have also resulted in the discovery of cases of active pulmonary disease among children in Kansas City, Missouri, and among student nurses in several states.<sup>9</sup> The pulmonary lesions simulated those of tuberculosis and eventually went on to calcification. There are no known criteria for differentiating these roentgenographic lesions and those of tuberculosis.

A review of the reported cases of histoplasmosis suggests that this is a highly fatal disease.<sup>10</sup> If the finding of positive reactors to histoplasmin is inter-

puted as evidence of infection with *Histoplasmosis capsulatum* or with some related organism, such a disease must be considered as existing chiefly in a benign and unrecognized form. Most workers who have been intimately concerned with these studies, however, are cautious in the interpretation of their findings,<sup>5</sup> partly because of the reports of cases of known and active histoplasmosis in which the skin tests with histoplasmin were negative<sup>9,10</sup> and particularly because of the demonstration of marked cross reactions with histoplasmin in animals with experimental mycotic infections, including blastomycosis, coccidioidomycosis and moniliasis.<sup>9,11</sup> The negative histoplasmin tests during active infection may be interpreted as evidence of anergy and are probably analogous to negative tuberculin tests in cases of miliary or other active forms of tuberculosis, they have been observed in severe disseminated and fatal cases of histoplasmosis.<sup>9,10</sup>

Histoplasmosis is not known to occur in New England, but it has been reported from areas as close as New York and Washington, D C. Unexplained pulmonary lesions, including disseminated areas of calcification, are encountered, however, that are not unlike those that have been described in Kansas City, Missouri, and Tennessee, which in those areas are associated with negative tuberculin reactions and positive cutaneous histoplasmin reactions. The possibility that some of these lesions in tuberculin-negative persons are the results of mycotic infections should be considered, particularly when other causes of disseminated pulmonary lesions can be excluded.

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## MASSACHUSETTS MEDICAL SOCIETY MEDICAL CARE FOR OLD-AGE ASSISTANCE

The following communication regarding rule relating to authorization and control of medical care for old-age assistance has been sent to all physicians in Boston by the Bureau of Old Age Assistance. It appears to be of sufficient importance to merit reprinting in the *Journal*.

Payment for doctor's service will be approved at a rate not to exceed \$3 00 for a home visit and \$2 00 for an office visit unless unusual circumstances warrant a higher payment.

Doctors are requested to notify the department immediately, to answer and return the medical inquiry promptly and to send bill to the recipient within fifteen days. Otherwise there may be a delay in payment.

Bills for excessive amounts and for an excessive number of visits and tardy bills are subject to review by the Medical Advisory Committee.

A rate not to exceed \$5 00 a day for hospital care will be approved subject to the department's agreements with the hospitals. This rate includes all care, including service of a physician. It is expected that recipients in need of hospital care will obtain care in the large incorporated hospitals where adequate and economical service can be obtained.

Each recipient of old age assistance proved eligible for the medical assistance will be given an additional grant in accordance with the need. The recipient is directly responsible to the doctor and the hospital for payment of the obligation incurred.

JOSEPH GARLAND, Secretary

#### DEATHS

DAVIS — Max Davis, M D, of Brookline, died April 30. He was in his forty-seventh year.

Dr Davis received his degree from Harvard Medical School in 1925. He was assistant professor of obstetrics and gynecology, Boston University School of Medicine, and senior visiting physician, Gynecological Staff, Beth Israel Hospital, and was a diplomate of the American Board of Obstetrics and Gynecology, as well as fellow of The American College of Surgeons.

His widow survives.

DUTTON — Frank K. Dutton, M D, of Springfield, died June 28. He was in his fifty-sixth year.

Dr Dutton received his degree from Tufts College Medical School in 1915. He was a fellow of the American College of Surgeons and the American Medical Association.

His widow survives.

GORHAM — George H. Gorham, M D, of Boston, died on March 12. He was in his seventy-seventh year.

Dr Gorham received his degree from Tufts College Medical School in 1903.

#### CORRESPONDENCE

##### SALT-FREE BREAD

To the Editor: In view of the known importance of low salt diets in the treatment of cardiac failure and also of hypertension, it appears to be important to call the attention of physicians in the vicinity of Boston to the fact that salt-free bread is now available through Betty Bakelite Incorporated, at one of their local stores (235 North Beacon Street, Brighton). The manager informs me that if the demand for this bread becomes great enough it will be supplied through their various stores throughout the city.

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## THERAPEUTIC ABORTION FOLLOWING RUBELLA

To the Editor: The progress article on rubella in the June 19 and 26 issues of the *Journal* was extremely interesting. The scientific approach to the etiology, course, differential diagnosis, complications, treatment and prevention was admirable.

The last three pages of the article, however might just as well have been deleted from a scientific journal of medicine. The discussion of therapeutic abortion in cases of rubella in early pregnancy was highly philosophical and thus controversial and definitely not scientific. In addition anyone with the slightest training in logic can discern numerous violations of ordinary common sense in this portion of the article.

Regardless of one's position in this disputed matter I repeat that discussions of this type do not belong in a scientific medical journal. If one has opinions or strong feelings on morality, euthanasia, the Bible or witches such opinions, it seems to me, should not be included in medical articles.

ALBERT E. PAGANINI M D

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Dr Paganini's letter was referred to Dr Conrad Wesselhoeft, the author of the article in question. His reply is as follows.

To the Editor: The criticism of the discussion of abortion in the progress review on rubella brings to mind a letter on the subject in the *British Medical Journal* (Barry W. K. Correspondence Rubella and pregnancy *Brit. M. J.* 1 423, 1947) that goes far beyond discerning 'numerous violations of ordinary common sense.' This English physician refers to abortion as murder and insists that as such this operation is never justifiable and, in the case of rubella in early pregnancy is a 'massacre of the innocents.'

The advancement of medical knowledge exerts a profound influence on public opinion and on the enactment of laws pertaining to human welfare. The mission of the medical profession is concerned not alone with scientific research and administering to the sick but also with preventive medicine. The carrying out of any preventive measures is dependent on enlightened public opinion and frequently involves overcoming deep-rooted beliefs. Vaccination against smallpox is a typical example.

In the discussion of the application of newer knowledge of rubella in early pregnancy, it seemed appropriate to bring out the historical background. The ancient concept that congenital defects resulted from witchcraft led me quite naturally to the original biblical commandment and to the evolution of laws pertaining to it. This approach assailed an ancient tenet that has been rendered obsolete through public opinion and the enactment of radical changes in the law.

The statutes relative to abortion have been amended to conform to our newer knowledge of disease without endangering the intent of the original law. After presenting the possibilities of congenital deformities following rubella in early pregnancy and the resulting unfortunate detriment to future pregnancies, I emphasized the purpose of the existing law and finished with an appeal for the consideration of a further amendment to cover this particular situation for the betterment of suffering humanity. The fundamental purpose of religion, medicine and the law is to help mankind. When this purpose fails, it is the fault of the frailties of human nature, and correction is due.

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## BOOK REVIEWS

*Agnesia, Apraxia, Aphasia Their value in cerebral localization* By J. M. Nielsen, M D. Second edition completely revised 84, cloth, 292 pp., with 59 illustrations. New York: Paul B. Hoeber Incorporated, 1946. \$5.00.

The elucidation of the many problems associated with speech defects has long been of interest to the medical profession. From the time of Broca through the work of Head in England and Starr and Mills in America, there has been

a continued interest in this problem. In recent years the outstanding investigator has been the author of this monograph. The first edition was published privately in 1936, when the enthusiasm for the study of aphasia and allied conditions was not great. The matter however, was kept open by the continued investigations of Dr Nielsen and his first publication did not fall on sterile ground. Indeed it was welcomed in many places where research was going forward. Now ten years later he has expanded the book into a second edition of increased usefulness.

In various chapters he covers a brief history of the knowledge of aphasia apraxia and agnosia. He then outlines the theories regarding causation of these conditions and details each in a separate section of the book. After giving the methods of examination used clinically in the elucidation of the signs of speech defects, he presents the bulk of his monograph in a careful analysis of the pathologic material observed by him over a period of many years and carefully correlated with the clinical evidence in each case. The volume closes with an appendix on nomenclature and a selected bibliography.

The book will be of use to the clinical neurologist who has to meet the acute problem of aphasia to the neurologic surgeon who needs to know the aphasic syndromes as an aid to localization and to the growing numbers of investigators who are attempting to untangle one of the most complicated of all problems in neurology. There is still much to learn, but no better basis for advancing knowledge can be found than the text provided by Dr Nielsen in the present edition of an outstanding monograph.

*Carbohydrate Metabolism Correlation of physiological biochemical and clinical aspects* By Samuel Soskin, M D and Rachmiel Levine, M D. 8" cloth 315 pp. with 42 tables. Chicago: University of Chicago Press 1946. \$6.00.

The authors state in the preface that 'the volume is intended to serve as a correlative text for the teaching of carbohydrate metabolism to students of physiology, biochemistry and medicine.' The average medical practitioner who consults the book may find a large part of it bewildering. He may feel beyond his depth as he reads the early chapters dealing with the 'enzymatic machinery' and other matters concerned with intermediary metabolism. Also, he will probably find many of the ideas that he has cherished regarding metabolism flatly contradicted.

The following quotation illustrates the iconoclastic attitude and diction of the authors:

It is clear that neither the low R.Q. of diabetes nor the failure of the R.Q. to rise following the administration of sugar constitutes evidence for a lack of ability to oxidize carbohydrate. One must conclude that chemical balance studies offer neither theoretical nor actual support for the R.Q. as a measure of dissimilation. Since no other validation of the R.Q. is available at the present time one must go further and say that there is no evidence that the R.Q. is a measure of dissimilation.

Concerning the dextrose nitrogen ratio they write, "We may summarize the present knowledge by saying that whatever its empirical usefulness the figure of 44-55 per cent commonly used in metabolic and nutritional work to calculate the carbohydrate equivalent of protein has no real basis of fact." In reference to ketosis they state:

It is thus no longer proper to speak of anti ketogenesis in the sense so long employed by clinicians by which they actually meant ketolysis (ketone oxidation). In view of present knowledge the various ketogenic, anti ketogenic ratios which have been used to calculate the amounts of carbohydrates necessary for oxidation of the ketone bodies must be regarded as being without any real significance.

Soskin has been a strong proponent of the theory that the fundamental metabolic defect in diabetes is overproduction of sugar contrary to the theory popularly held in the past that there is a loss of the capacity to utilize sugar. The work that he and his collaborators have done to support this view and to develop new ideas regarding carbohydrate metabolism is discussed in detail. In presenting controversial points Soskin has tried to be impartial but his critics may claim that he has not always succeeded.

The direct clinical applications of the book are limited. Indeed, such clinical recommendations as the use of the intravenous glucose-tolerance test as a criterion of liver function and the opinion of the authors concerning the alleged need for large amounts of sugar or other carbohydrates in the treatment of diabetic coma are not likely to receive general acceptance.

Progress in medical practice cannot be made unless there is readiness to relinquish unsound concepts. Soskin and Levine will give a healthy stimulus to those whose ideas are fixed by prejudice or misinformation.

*The American Hospital*. By E. H. L. Corwin, Ph.D. Studies of the Committee on Medicine and the Changing Order, New York Academy of Medicine. 8°, cloth, 226 pp. New York: The Commonwealth Fund, 1946. \$1.50.

In this special monograph Dr. Corwin presents a factual analysis of existing hospital conditions in the United States. He points out that although the present hospital plant represents an investment of five and a half billion dollars it has reached this magnitude through unorganized effort and not by conscious planning.

The first chapter reviews briefly the history of hospital information from the time of the first list, compiled by Dr. J. M. Toner in 1873, to the present. The second discusses the hospital domain, embracing the development, types and ownership of hospitals. It is well documented with charts and tables. The statistics for 1943 show a total of 6655 hospital institutions of all kinds in the country, with a total bed capacity of 1,649,254 — or about 1 hospital bed for every 80 persons in the gross population. One of every 10 persons in the United States is admitted annually to a hospital. The third chapter deals with hospital finance and analyzes plant assets, investment sources, including the increasing governmental participation, operating costs and income from various sources. The succeeding chapters discuss the distribution and utilization of hospital facilities, the hospital as employer and as a training ground, personnel and administration, medical service and the outpatient department and the housing of hospitals.

The uneven distribution of hospital facilities is analyzed, and the effect of urbanization and industrial centralization is emphasized. Efforts to increase and improve hospital facilities, including prepayment plans, Blue Cross, workmen's compensation, inclusive-rate and moderate-rate plans, are gone into in detail. Medical service is discussed from the viewpoints of organization and standardization.

In the final chapter, under the heading "Retrospect and Prospect," an attempt is made to summarize the significant facts brought out in the previous chapters and to examine the future of the hospital. The topics discussed include the importance of the general hospital, dependence of local governments on voluntary hospitals, nonprofit basis of hospital investment, size of hospitals, rising costs and cost accounting, sources of revenue, utilization of hospitals, domiciliary care of sick patients, chronic and convalescent, estimate of postwar needs, research, public-health and preventive medicine and pathometry, or the use of hospital statistics.

A list of selected references is appended to each chapter, and a good index concludes a well published volume. It contains a mass of authoritative data, and is recommended for all medical libraries as well as public libraries and hospital administrators.

*The Second Forty Years*. By Edward J. Stieglitz, M.D. With a foreword by Anton J. Carlson, Ph.D., LL.D., M.D., Sc.D. 8°, cloth, 317 pp., with 18 figures. Philadelphia: J. B. Lippincott Company, 1946. \$2.95.

In this semipopular book Dr. Stieglitz presents a guide to longer life and considers the problems incident to the aging of the person over forty. The biology and hazards of senescence are comprehensively discussed. It is interesting to note that the average life span has increased from twenty-one years at the time of the Holy Roman Empire to sixty-six years in 1944.

The rate of aging is rapid from birth to forty years, and slows from forty to a hundred years, on a chart it is almost a straight drop to twenty years, and about a flat line from fifty years on. Statistical graphs point out an interesting

situation in 1900, persons of sixty-five years and over comprised 4.1 per cent of the population, in 1940, the figure had increased to 6.8 per cent, and it is estimated that in 1980 the percentage will have increased to 14.4. The percentage of persons under five years of age during the same periods are, respectively, 12.1, 8 and 6.4. The life expectancy from birth was forty years in 1850, forty-seven years in 1900 and sixty-three years in 1940, and if the increase continues at that proportion to 1980 the span may reach seventy to seventy-five years. These statistics reveal a decline in the birth rate and an increase in the life span, a serious problem.

There are special chapters on heart disease, high blood pressure, cancer, nutrition, sex and age, mental changes and the wise use of leisure. The final chapter discusses the relation of an aging people to society.

The book contains practical advice for the elderly on how to eat, play, think and face the threats of chronic disease. It is an unusual, outstanding treatise by a competent medical authority and should be in all libraries, medical and public. The volume is well published in every way.

*The Chest. A handbook of roentgen diagnosis*. By Leo C. Rigler, M.D. 8°, cloth, 352 pp., with 338 illustrations. Chicago: Year Book Publishers, Incorporated, 1946. \$6.50.

The greatest limitation in the atlas type of presentation of radiologic texts has been the poor quality of reproduction. In this volume the problem is well handled in handbook form. The illustrations are numerous and of good quality and are captioned by descriptions and interpretations of specific examples of roentgenologic changes in diseases of the lungs, bronchi, mediastinum and pleura. Primary heart changes and lesions of the thoracic cage have been omitted since they are outside the scope of the book. The pathological and physiologic aspects of diseases of the chest are discussed only so far as they are relevant in roentgenologically evident lung changes.

The presentation is sound, and the descriptions are lucid; the organization for reference, however, is poor, and the book is not inclusive enough for a reference on chest disease.

In the field of chest diagnosis, in which the roentgenologic interpretation stands unrivalled as the most rewarding single procedure, the internist should find this book an elucidating text and a helpful guide. The student of roentgenology will also find it excellent for preliminary orientation.

*Mongolism and Cretinism. A study of the clinical manifestations and the general pathology of pituitary and thyroid deficiency*. By Clemens E. Benda, M.D. 8°, cloth, 310 pp., with 101 illustrations and 48 tables. New York: Grune and Stratton, 1946. \$6.50.

This monograph is based on the study of a large series of cases of mongolism and cretinism seen at a state school for mental deficiency. The study covers all aspects of both diseases in an adequate, scholarly manner and thus brings to the attention of physicians a complete review of present knowledge of the two distressing conditions. Most of the book deals with mongolism, and the conclusions are based on the observations of more than 300 patients. Dr. Benda adds greatly to knowledge of the hereditary aspects of the problem, as well as its relation to the pregnancy of the mother and the order of birth. He believes that mongolism is due to deficiency of the anterior portion of the pituitary gland — a point that is not conceded by many investigators. Factors other than endocrine are needed to explain all the aspects of mongolism. Moreover, treatment by glandular preparations has not been satisfactory, even in Dr. Benda's hands.

The format of the book, the illustrations and the bibliography are beyond criticism. The monograph will be of particular interest to pediatricians and obstetricians.

*Introduction to Surgery*. By Virginia K. Frantz, M.D., and Harold D. Harvey, M.D. 12°, cloth, 216 pp. New York: Oxford University Press, 1946. \$2.50.

This is a pocket-sized volume with an excellent index and extensive up-to-date references. Well adapted for the beginner, it is concise and clear and presents the elements of surgery in a simple, readable manner. It is especially recommended for medical students.

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## SEPTICEMIA DUE TO *SALMONELLA ENTERITIDIS*

MILES P. BAKER, M.D.,\* AND JOSEPH H. BRAGDON, M.D.†

BOSTON

THE genus *Salmonella* comprises a large number of gram-negative enteric bacilli pathogenic to both man and animals. They are grouped together by reason of similarities in biochemical behavior, but more definitively by reason of the specific antigens that they possess in common. Differentiation within the group is based on variations, often minor, in these biochemical and antigenic characteristics. The National *Salmonella* Center has available for distribution over one hundred and sixty different species or types, not all of which, however, have yet been proved pathogenic to man.<sup>1</sup>

In the accepted classification *Salmonella enteritidis* falls into Group D, for its somatic antigens are identical with those of *Eberthella typhosa*. In most respects, however, it more closely resembles other members of the genus. It has a wide natural distribution, having been isolated from a variety of animals, both wild and domestic, in many parts of the world. Human infections with *S. enteritidis* usually arise from the ingestion of uncooked material from infected animal sources. Persons thus contracting infection with this organism characteristically develop nonbloody and nonpurulent diarrhea accompanied by varying degrees of abdominal pain, nausea and vomiting. Prostration may be alarming, but the symptoms are short lived, and recovery is complete.

*S. enteritidis* was first isolated in 1888 by Gärtner,<sup>2</sup> who recovered it following an outbreak of acute gastroenteritis that had affected 58 persons, all of whom had eaten meat from an emergency-slaughtered cow. Known since that time as Gärtner's bacillus, it has frequently been responsible for similar outbreaks of food poisoning. In 1926 Kinloch et al.<sup>3</sup> reported an outbreak of acute gastroenteritis in Aberdeen affecting 497 persons, all of whom had drunk milk subsequently traced to a single cow. *S. enteritidis* was isolated from the cow's udder, from samples of the milk and from the stools of many of the victims. According to Topley and Wilson,<sup>4</sup> *S. enteritidis* was responsible

for over 12 per cent of all outbreaks of food poisoning produced by *Salmonella* in England between 1923 and 1939. It was exceeded in incidence only by *S. typhimurium*. An analysis by Edwards and Bruner<sup>5</sup> of data accompanying organisms submitted to the National *Salmonella* Center indicates that it has been somewhat less frequent in the United States.

Although *S. enteritidis* has definite invasive powers for the tissues of mice and of other laboratory rodents, in human infections it is not prone to penetrate beyond the intestinal mucosa. It is true that Gärtner originally isolated the organism from the spleen of the one fatal case in his series, but comparable cases with adequate bacteriologic confirmation are extremely rare. The literature contains several reports of isolated cases in which *S. enteritidis* was reputedly recovered from the blood stream, but it is likely, as Topley and Wilson<sup>4</sup> point out, that many of these were actually cases of infection with *S. dublin*, whose differentiation is of comparatively recent date. Confusion caused by failure to distinguish the two organisms occurred as late as 1944, when, in an article entitled "*Bacterium enteritidis* Septicaemia," McDonald<sup>6</sup> reported 3 cases of prolonged fever—one of which was fatal—in Indian soldiers. In each case *S. dublin* was isolated from the blood.

Authenticated cases in which *S. enteritidis* has been recovered from sites other than the gastrointestinal tract are, nevertheless, to be found. Of a thousand consecutive *Salmonella* organisms (exclusive of *E. typhosa*) submitted to the New York *Salmonella* Center thirty-one were identified as *S. enteritidis*. Seligman, Saphra and Wassermann,<sup>7</sup> in analyzing this material, reported that in 25 cases the organism had originally been isolated from stools, but that in 4 it had been recovered from the blood and in 2 from abscesses, in 1 it had been the cause of a purulent meningitis. Clinical case reports in which *S. enteritidis* has exhibited invasive qualities are confined largely to infants, among whom the organism appears to have a predilection for the meninges. Guthrie and Montgomery<sup>8</sup>

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reported a nursery epidemic involving 27 infants. In 15 cases the organism penetrated the body beyond the intestinal tract, producing a purulent meningitis in 10.

Among adults *S. enteritidis* appears to gain access to the blood stream only when the natural resistance of the host has been lowered by concomitant diseases. Savino and Menendez<sup>9</sup> identified the organism following isolation from the blood of 10 soldiers in the Chaco War. Clinical data in their paper are extremely scanty, but the patients were apparently suffering from a condition similar to typhoid fever. The authors emphasize the point that the troops were severely debilitated by other conditions. Huang et al.<sup>10</sup> reported 17 cases of bacteremia due to *S. enteritidis* among the beggars of Peking. In 9 cases the infection occurred simultaneously with relapsing fever, and in all the authors emphasized the poor general health of the patients.

During the fighting in the Buna-Sanananda area of New Guinea in December, 1942, and January, 1943, a considerable but unknown number of American and Australian troops became infected with *S. enteritidis*. In several cases the organism penetrated beyond the gastrointestinal tract, producing fevers and suppurative processes of considerable clinical interest. It is the purpose of this paper to report 6 cases among American troops, all of whom were seen at a United States Army general hospital at various times following the close of the campaign.\*

### CASE REPORTS

**CASE 1** About January 29, 1943, while in combat at Sanananda, this patient developed fever and headache. He was hospitalized. Because of the finding of a positive smear for malaria (type undetermined) and an enlarged spleen, he was given antimalarial therapy. A temperature up to 105°F continued. At the end of the 1st week of fever the left testicle became painful, simultaneously with the onset of a mild degree of frequency and dysuria.

The patient was evacuated to Australia and on February 24 was admitted to the hospital, exhausted and apathetic. His chief complaints at that time were diarrhea and testicular pain. The temperature was 102.4°F, and the pulse 90. Physical examination revealed an enlarged spleen and a swollen, tender left epididymis. Examination of the blood disclosed a hemoglobin of 60 per cent and a white-cell count of 7000, with a normal differential count. Smears were negative for malaria. The urine persistently showed many polymorphonuclear cells in the sediment. The stools were liquid but not purulent. Although no diagnosis was made, sulfathiazole was given, following which the fever, diarrhea and epididymitis subsided.

On March 3 the patient first complained of pain over the fifth costal cartilage on the right, and during the following 10 days a subcutaneous mass gradually developed in this area. The mass was firm and tender, and the overlying skin was reddened. It was aspirated and from the thin purulent material obtained *S. enteritidis* was isolated in pure culture.

The general condition had continued to improve, but on April 7 the patient again began to have daily elevations in

temperature. The right femoral lymph nodes became moderately enlarged and tender. The white-cell count rose to 22,850, with 31 per cent eosinophils, but this was presumably related to the subsequent appearance of hookworm ova in the stools. A blood culture taken on April 13 grew *S. enteritidis*, but one taken on the following day remained sterile. A stool specimen submitted on April 24 was positive for the same organism, and sulfadiazine therapy was begun. The drug was continued for 3 weeks and was associated with a steady decrease in the temperature and a reduction in the size of the femoral nodes. *S. enteritidis*, however, continued to be passed in the stools. The patient was given sulfa guanidine for 16 days, after which repeated cultures remained negative.

The only problem then remaining was a chronic draining sinus on the chest wall, which had been present since a biopsy of the abscess had been taken in April. On August 25 the sinus was explored. It was found to lead into a cavity in the fifth costal cartilage. Six centimeters of cartilage was removed. The wound healed slowly, continuing for some time to give positive cultures for *S. enteritidis*. The patient was not returned to duty until November, almost 10 months after the appearance of the first symptoms.

In March, 1944, the patient was readmitted to the hospital for an unrelated condition. The sinus on the chest wall had remained closed. Two stool cultures were examined for *S. enteritidis* with negative results.

**CASE 2** This soldier, from the same company as the patient in Case 1, had been in the combat area at Sanananda from December 28, 1942, to January 9, 1943. On January 20 he had his first chill and a fever that did not respond to the usual therapeutic doses of quinine. He was therefore admitted to a hospital, where, because of an enlarged spleen and a smear that was said to have been positive for *Plasmodium vivax*, quinine was continued in large doses. The patient became progressively worse, developing a severe diarrhea, a painful right epididymis and, eventually, delirium. He was evacuated to Australia and admitted to the hospital on February 24.

On admission he was febrile. The spleen was enlarged and tender. The right epididymis was markedly swollen and tender. The white-cell count was 5650, with a normal differential. No malaria parasites were found. The patient was treated supportively. The diarrhea soon relented, but left sided pleuritic pain developed. Rales were heard over the left lower lobe, and an x-ray film confirmed the diagnosis of pneumonitis as well as showing a small pleural effusion. Sulfathiazole was given without effect. Not until March 25 did the patient become afebrile—for the first time in 9 weeks—and begin to improve in weight and well-being. The epididymitis subsided spontaneously.

On April 23 he complained of the sudden onset of severe pain low in the back. About 2 weeks later chills and fever reappeared. *P. vivax* was again demonstrated in the blood, but in spite of intensive antimalarial therapy the fever continued for 4 or 5 weeks. Physical and x-ray examination revealed no localizing signs of infection in the lumbar vertebrae. Because of experience with other cases of infection with *S. enteritidis* this organism was specifically sought in the blood, stools and urine, but with negative results. A specimen of serum drawn on May 30, however, agglutinated the organisms recovered from other cases of infection in dilutions of 1:320.

By June 15 the second febrile episode had terminated, and the patient began to regain the 25 pounds of weight that he had lost. He continued, however, to complain of severe low-back pain, and the sedimentation rate remained elevated. It was not until August 16 that there were any radiographic changes to explain these phenomena. At that time definite narrowing of the intervertebral spaces between the fourth and fifth lumbar vertebrae, with partial destruction of the posterior portions of the vertebrae, was observed. In view of the clinical course and the high agglutinating titer of the serum it was believed that *S. enteritidis* was the organism responsible for the bone infection. The patient was immobilized in a plaster shell, with considerable relief of pain, and evacuated to the United States. The subsequent course of the illness is not known.

\*Fourteen similar cases<sup>11</sup> were observed in an Australian general hospital at Port Moresby from January to March, 1943. The patients had been evacuated from the same small combat area from which the following cases had been derived. The predominant clinical picture was that of empyema, peritonitis and perichondritis (costal cartilage) or subcutaneous abscess. *S. enteritidis* was recovered from the blood, urine, stools and abscesses. In 1 case the soldier had been out of the combat area for a month before the onset of the febrile illness.

CASE 3 In early January, 1943, while in a field hospital near Buna convalescing from a minor gunshot wound received a month previously, this patient had diarrhea and fever for 4 or 5 days. On January 10 malarial parasites (type undetermined) were found in the blood but despite specific therapy the fever continued unabated for another 12 days. At that time an area of local tenderness on the right lower chest anteriorly was noted. Occasionally a sharp pain was present in the same region. All symptoms however including the fever gradually subsided.

In February cloudy vision developed in the left eye, and the patient was evacuated to Australia, entering the hospital on the eye service on February 25. Examination revealed fine vitreous opacities with an area of acute chorioretinitis. The eye slowly responded to local treatment.

It was not until April 1 that attention was directed to a tender mass overlying the costochondral junction of the right eighth rib. This corresponded in location to the previous attack of pain and tenderness. In other respects the patient felt entirely well and was afebrile. On April 25 the mass was aspirated, yielding a small amount of purulent material from which *S. enteritidis* grew in pure culture. Three urine and six stool cultures were negative for the same organism. Sulfadiazine was given for 3 weeks, following which the mass resolved. The patient was discharged to duty in July.

CASE 4 This soldier was in combat in the Buna-Sanananda area from December 5, 1942, to February 4, 1943. His company being for a time close to that of the patients in Cases 1 and 2. During this period he had two bouts of malaria, both of which quickly responded to specific therapy and one attack of mild diarrhea for 6 days. Following the campaign his unit was returned to Australia. The patient was active on training maneuvers until March 26, when he developed pain in the left shoulder and 2 days later chills fever abdominal pain and vomiting. He was admitted to a hospital where malarial parasites were found in the blood. Despite specific therapy the temperature continued to swing daily up to 103°F. The white-cell count remained under 10,000, with a normal differential. Sulfadiazine had no effect on the fever. Finally, a tender mass appeared in the left upper quadrant of the abdomen and the patient was transferred to a general hospital on April 18.

On admission the patient was febrile. In addition to a grapefruit sized mass in the left upper quadrant a soft tender mass was palpable in the rectovesical pouch. The white-cell count was 5600. On April 22 the pelvic abscess was evacuated through the anterior rectal wall, and the left upper quadrant mass, which was found to be a well localized peritoneal abscess, was incised and drained. From the latter *S. enteritidis* was isolated in pure culture.

Following surgical drainage there was a prompt cessation of fever. Blood and urine cultures taken during the following week were sterile, but from two of several stool specimens the same organism was isolated. The patient made an excellent recovery and the surgical wound healed without evidence of residual infection. Following sulfaguanidine therapy for 11 days, *S. enteritidis* disappeared from the stools.

CASE 5 This patient was in the Buna-Sanananda area from December 25, 1942 to February 12, 1943. During that time he had no diarrhea but did have two attacks of fever both of which responded to specific antimalarial treatment. In June, while on furlough in Australia, he developed chills, fever and severe backache. Antimalarial treatment had no effect on the symptoms. He became extremely ill, confused and irrational. On June 26 he was transferred to the hospital.

The temperature rose almost daily to 103°F. Physical examination revealed only a palpable spleen and severe low back pain with muscle spasm. The white-cell count was 5700, with a normal differential. The urine showed moderate numbers of polymorphonuclear cells. Despite negative smears for malarial therapeutic doses of quinine and quinaquine (Atabrine) were given, but without effect on the fever. Blood agglutination studies were performed and the serum was found to agglutinate *S. enteritidis* in a dilution of 1:640. The organism was then isolated from the urine and from the stools. Although "rose spots" appeared on the abdomen blood cultures remained sterile.

On July 27 sulfaguanidine therapy was instituted. Stool and urine cultures soon became negative, and the tempera-

ture returned to normal. X ray films taken on August 2 showed a destructive process in the body of the fourth lumbar vertebra. The patient remained afebrile but because of pain he was immobilized in a plaster shell and evacuated to the United States. The subsequent course of the illness is not known.

CASE 6 This patient was in the Buna-Sanananda area from late November to late December, 1942. In the latter month he had two mild attacks of diarrhea and on December 26 a bout of malaria with a positive smear which responded promptly to specific therapy. He had two further attacks of malaria one in January and one in March, 1943, both of which responded satisfactorily to treatment.

On April 8 while on duty in Australia he developed pain and swelling in the left testicle. He was afebrile, and there were no systemic symptoms. He was admitted to a hospital, where he received sulfadiazine and applications of ice to the testicle. The pain and swelling gradually subsided, and he was returned to duty. Two days later the same symptoms recurred.

On admission to a general hospital on May 7 he was afebrile. Physical examination revealed no abnormalities other than a tender moderately enlarged left testis, with some thickening of the cord. Routine laboratory examinations were negative. The white-cell count was 9000.

On May 13 an orchidectomy was performed. The testis was found to be distended by a large abscess filled with thin gray fluid. *S. enteritidis* was isolated in pure culture from the exudate. Blood and urine cultures were then taken and proved sterile, but on several occasions the stools were found to contain the same organism. Sulfaguanidine therapy was accordingly administered and was followed by the disappearance of the organism from the stool. Complete healing of the surgical wound occurred and the patient was discharged to duty on October 6.

## BACTERIOLOGY

Salmonella organisms grow readily on ordinary bacteriologic mediums, and in most cases a tentative identification can be made within a few days by

TABLE 1 Sources of *S. enteritidis* and Maximum Serum Agglutinin Titers

Case No.	SOURCE				MAXIMUM TITERS
	BLOOD CULTURE	URINE CULTURE	STOOL CULTURE	ABSCESSES CULTURE	
1	Positive	Negative	Positive	Positive	1:2560
2	Negative	Negative	Negative	—	1:320
3	—	Negative	Negative	Positive	1:2560
4	Negative	Positive	Positive	Positive	1:640
5	Negative	Positive	Positive	—	1:640
6	Negative	Negative	Positive	Positive	1:60

fermentation reactions and simple group-agglutination tests.\* Definitive identification within the group, which depends on minor variations in antigenic structure, should be delegated to laboratories specifically equipped for such work†

Table 1 presents the various sources from which the organism was recovered in each case. It should be realized that cultures were rarely taken during

\*The biochemical reactions were constant in all cases. The organisms promptly fermented the 4-11 ring sugars with the production of acid and gas; dextrose, maltose, mannitol, xylose, arabinose, rhamnose, a d-sorbitol. Dulcitol was fermented only after four or five days. Lactose, saccharose, inositol and inulin were not fermented. The organisms produced large amounts of hydrogen sulfide. It did not produce indole or H<sub>2</sub>S gelatin.

†We are indebted to Dr. Erich Seligmann of the Department of Bacteriology, Beth Israel Hospital, New York City who determined the antigenic structure of the organism.



periods of the infection in which positive results were likeliest to occur — that is, they were obtained for the most part late in the course of the disease

In a case of vertebral abscess (Case 2) the diagnosis was based only on the presence of a high agglutinin titer in the serum. One might question whether this case should have been included, but because the clinical course was similar to that in Case 1, we consider inclusion justified, although the organism was not isolated.

The antigen for the agglutination tests was prepared from freshly isolated strains suspended in 0.5 per cent phenol in physiologic saline solution. In each case the serum gave a flocculent ("flagellar") type of agglutination. As would be expected by reason of common somatic antigens, O strains of typhoid bacilli were also agglutinated by these serums in high dilution.

### EPIDEMIOLOGY

Data concerning the number of troops affected in this outbreak of *S. enteritidis* infection are unobtainable, because in most cases the symptoms were probably mild and because, in the exigencies of bitter jungle fighting, many men failed to report diarrheas and even fevers that were not incapacitating, nor were adequate diagnostic facilities available at the front.

Although the evidence is not conclusive, it seems likely that the majority of infections were contracted from the same source and at about the same time. All the cases presented above did not occur in the same company, but they occurred in the small Buna-Sanananda area of the jungle for varying periods during December, 1942, and January, 1943. For three days — that is, from December 25 to 27 — 5 of the 6 patients were there simultaneously. It seems reasonable to assume that infection took place at or about that time. To our knowledge no subsequent cases of infection with *S. enteritidis* occurred elsewhere as the campaign progressed in New Guinea.

Nor have we any definite evidence regarding the source of the outbreak. It appears unlikely that infection occurred from the ingestion of food products from infected animals — the usual source of *Salmonella* outbreaks — since the diet of the troops was limited entirely to C rations, which consisted of dried and tinned food processed in the United States. Infection may have originated from a carrier of the organism among Allied or enemy troops or from one of the native bearers. Rats have been known to harbor the organism,<sup>12</sup> and there were many rats in the area.

The infection was probably transmitted through contaminated drinking water. Water was obtained from the corpse-strewn, rat-infested swamps in which the troops fought. Boiling was rarely possible, and individual chlorination was at best haphazard. The epidemic may have been fly-borne, for flies

were plentiful. Excreta were usually deposited where circumstances permitted.

### DISCUSSION

In a recent review of *Salmonella* infections, Bornstein<sup>13</sup> describes the following clinical syndromes resulting from human infection with these organisms:

*Salmonella gastroenteritis* The essential features are the abrupt onset of vomiting and nonbloody diarrhea eight to thirty-six hours after the ingestion of contaminated food or water. There may be slight fever for a few days, but there is usually prompt recovery.

*Salmonella fever* A typhoid-like course, leukopenia, splenomegaly, abdominal pain and occasionally vomiting and diarrhea occur. The disease is generally milder and less typical than that caused by *E. typhosa*. Blood cultures are positive early in the disease.

*Salmonella septicemia* Impressive invasion of the blood stream is usually present from the onset of a high remittent fever. Localization of the infection through hematogenous dissemination is likely and spares few structures. Bronchopneumonia, osteomyelitis, meningitis, pyarthrosis and endocarditis are not rare.

Bornstein stresses the point that on occasion any *Salmonella* may produce one of the syndromes listed above. The clinical course in the cases reported above was far different from that in the simple gastroenteritis usually produced by this organism. In 5 cases there was prolonged fever simulating that seen in infections caused by *E. typhosa*, an organism with which *S. enteritidis* shares common somatic antigens. In all cases there were prominent suppurative features such as are occasionally seen in infections with Group C *Salmonella* organisms, particularly *S. choleraesuis*.<sup>14</sup>

Lack of familiarity with the natural history of *Salmonella septicemia* and its sequelae led to delay in diagnosis in most of the cases. In none was the diagnosis made on admission to the hospital. In retrospect, however, survey of the clinical features brings out certain distinctive characteristics.

The 6 patients may be separated into two groups: those who developed a sustained nonmalarial fever and evidence of blood-stream invasion while in the combat area, where opportunity for this infection was present, and those who had no characteristic symptoms of *Salmonella* infection until suppurative lesions manifested themselves three to six months after the patient had left the combat area. This prolonged period of asymptomatic infection was the striking feature in the latter group of cases, but even in the first group the sometimes indolent character and always insidious development of suppurative lesions were noteworthy. In Case 1 five weeks had elapsed and the initial fever had abated before the appearance of subcutaneous swelling overlying

a costal cartilage indicated the presenting abscess. The patient in Case 2 had been convalescent for four weeks after nine weeks of fever, pneumonitis and urinary-tract infection when he developed excruciating pain in the back and a recurrence of fever that lasted for five weeks. X-ray examination ultimately revealed destructive changes in two lumbar vertebrae. Case 3 illustrates an earlier appearance of symptoms referable to localized infection, but the abscess was long in developing to a conspicuous degree. This patient noted a tender area on the anterior aspect of the chest wall during his initial twelve-day fever. It was not until three months later that a suppurating mass appeared in the area and gave the first opportunity for correct diagnosis.

Cases 4 and 5, in the second group, closely resembled Case 2 except that the patients did not have a sufficiently prolonged initial fever to warrant hospitalization. As in Case 2 the subsequent onset of symptoms of localized *Salmonella* infection was accompanied by fever. In Case 4 the association of the fever with a normal white-cell count and pain in the left upper quadrant and shoulder led to a tentative diagnosis of malaria despite the absence of parasites in the blood smears. Antimalarial treatment was unavailing. It was not until an abscess presented and was drained that the diagnosis of *Salmonella* infection was established and its tendency to manifest itself in localized suppuration was recognized. Again, in Case 5, the backache was at first erroneously attributed to malaria without due consideration for the severity of the pain and with delay in obtaining x-ray evidence of osteomyelitis of the lumbar spine. Case 6 was unique in that the slow development of a testicular abscess was not associated with fever.

The propensity of the patients to develop recurrences of fever is noteworthy. Fever usually reappeared in association with the suppurative lesions. In Case 1 the blood culture was positive for *S. enteritidis* during the relapse. The second febrile episode in Cases 4 and 5 may well have represented recurrences of bacteremia also.

The likelihood of genitourinary-tract infection in the early stage of bacteremia is borne out by the presence of epididymitis in Cases 1 and 2, positive urine cultures for the organism in Cases 4 and 5 and the development of a testicular abscess in Case 6.

The localization of infection in the costal cartilage in 2 cases bears an interesting similarity to the behavior of other *Salmonella* infections. Ssokoloff<sup>15</sup> described 10 cases in which *S. choleraesuis* produced a costal chondritis. The cases occurred during the Russian typhoid-paratyphoid epidemic of 1919-1923

and were generally associated with a "paratyphoid relapse."

Various sulfonamides have been reported of value in the treatment of *Salmonella* infections. No definite conclusions, however, can be drawn regarding the efficacy of sulfonamide therapy in the cases presented above. Different drugs were administered in varying dosages for arbitrary periods during the infections. In only 1 case (Case 2) did a sulfonamide appear to exert no beneficial effect whatever.

In 4 cases a stool-carrier state developed. In each case the organism disappeared from the stool following sulfaguanidine in doses varying from 3 gm every four hours to 3 gm every eight hours, continued for several weeks. But this apparent success must be interpreted in light of the observation that convalescent *Salmonella* carrier states usually terminate spontaneously in a matter of weeks.<sup>12</sup>

### SUMMARY

An outbreak of infection caused by *Salmonella enteritidis* among troops in the Papuan campaign in New Guinea is reported.

In some cases the disease progressed far beyond the acute gastroenteritis usually associated with infections caused by this organism. Six cases seen in a general hospital with late manifestations of the infection are presented. In 5 the infection was associated with a condition similar to typhoid fever. All cases eventually developed focal suppuration.

The cases serve to illustrate the recent concept of the protean nature of *Salmonella* infections.

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## FAMILIAL HEMORRHAGIC TELANGIECTASIA\*

## With a Note on the Use of Oxidized Cellulose Gauze as a Hemostatic Agent in Epistaxis

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THE occurrence of epistaxis in association with developmental anomalies of the blood vessels was first mentioned by Sutton<sup>1</sup> in 1864. Babington<sup>2</sup> described hereditary epistaxis in 1865. Thirty-one years later Rendu<sup>3</sup> reported the same condition in a patient with cutaneous angiomas. The classic monograph of Sir William Osler<sup>4</sup> in 1901 on a form of familial recurrent epistaxis associated with multiple telangiectases of the skin and mucous membranes did much to establish the syndrome as a clinical entity. Weber<sup>5</sup> presented an account of another case of this rare disorder in 1907. Today, the Rendu-Osler-Weber disease, often referred to as Osler's disease, is known as familial hemorrhagic telangiectasia.

Although there is reason to believe that this disease occurs much more frequently than the number of reported cases indicates, about 500 patients in more than a hundred families have been described in the literature up to the present time. The disease occurs equally in both sexes, and is transmitted as a simple dominant by both men and women. Win-trobe<sup>6</sup> states that families of the following stocks are affected in the order indicated: Anglo-German, Latin, Scandinavian and Jewish.

The cause of this morbid derangement of the capillaries is unknown, but the condition has been placed in the nondescript group of disorders often referred to as exhibiting degenerative stigmas. Teahan<sup>7</sup> has traced the disease in six generations of one family. Since severe bleeding does not begin until the fourth or fifth decade, it has been thought that an endocrine factor at least aggravates the bleeding tendency. The results of estrogenic therapy have not supported this belief. Arteriosclerosis and aging processes may contribute to the hemorrhagic proclivity, but even here the evidence is not too convincing. It is interesting to note that Singer and Wolfson<sup>8</sup> found increased capillary fragility as evidenced by a positive tourniquet test in their study. These authors link the disorder to hereditary familial vascular purpura. Wells<sup>9</sup> reported 2 cases of the disease with a prolonged bleeding time, in one of which the patient showed increased capillary fragility. As a result of these findings Wells believes that the disease also overlaps von Willebrand's<sup>10</sup> pseudohemophilia. Familial hemorrhagic telangiectasia, hereditary familial vascular purpura, and pseudohemophilia, together with familial epistaxis

without telangiectasia, may stem from a common hereditary vascular dysplasia. With the present unsatisfactory classification of these diseases in mind, these disorders are reviewed in the light of newer physiologic and anatomic findings.

The telangiectases have been known to occur in almost every organ of the body. On the skin they appear as small violaceous spots 0.1 to 3.0 mm in diameter. Spider telangiectases are sometimes visible on the face, and large vascular nevi covering the nose have been reported.<sup>11</sup> On the nasal mucosa the small reddish purple spots dot the septum and floor of the cavity. They may be seen on the tongue and oral mucosa. Lesions have been reported in the stomach on gastroscopic examination<sup>12</sup> and have been confused with ulcer, with which they may be associated. Telangiectasia of the lungs may be a more frequent cause of pulmonary hemorrhage than is ordinarily thought. Hematuria has been described by continental writers,<sup>13</sup> and it is well to inquire carefully about familial bleeding in cases of essential hematuria in patients over forty years of age. The lesions of the skin are not always permanent as has been stated in the literature. In the case reported below, the telangiectases were often absent at various examinations. Hepatomegaly, splenomegaly and increasing intolerance to blood transfusions of Type O have been reported by Fitz-Hugh.<sup>14</sup> The blood picture in cases of familial hemorrhagic telangiectasia is normal, except for the posthemorrhagic anemia that results from the repeated bleeding. The microscopical features of the disorder have often been commented on.<sup>15, 16</sup> The terminal vessels, capillaries and venules are dilated and thinned. Covered by a scanty layer of epithelium, these thinned and dilated vessels are either easily traumatized or else ruptured by some unknown intrinsic factor, with resultant bleeding. It can be seen, then, that the disease is inherently a capillary disorder. Hemorrhage is usually associated with lesions of the nasal mucosa.

The typical telangiectases may be found early in life, but they seldom cause serious hemorrhage until the patient reaches the fourth decade. Epistaxis then becomes increasingly troublesome and serious as age advances. Many patients have the lesions but not the bleeding tendency. This, together with atavism,<sup>17</sup> may explain, to some extent, the absence of the disease in some generations of a family. Repeated hemorrhage—usually epistaxis—in either sex at about the fourth decade or after, a positive

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family history of bleeding and the presence of telangiectases on the skin and mucous membranes, particularly the nasal mucosa, suggest the diagnosis of familial hemorrhagic telangiectasia. The typical blood dyscrasias are usually excluded by the presence of normal blood physiology.

The most serious complication of the disease is fatal hemorrhage. The mortality from hemorrhage per se is given as 3 to 6 per cent by various authors. Most of the patients with familial hemorrhagic telangiectasia harbor a secondary anemia from the repeated blood loss. It is surprising how well they adapt themselves to this posthemorrhagic state

results. Some students of the disease think that snake venom helps to control the bleeding. Styptics and thromboplastin are of temporary value when applied locally in conjunction with pressure or a nasal pack. I have found a latex finger cot tied around the end of a catheter and inflated, to be a useful aid in maintaining hemostasis preparatory to the insertion of a nasal tampon. Radiation may induce a remission of one to three years, but it is reported to have caused destruction of the septum. No physician who has observed these patients after repeated and thorough cauterization can conscientiously say that he has been tremendously im-

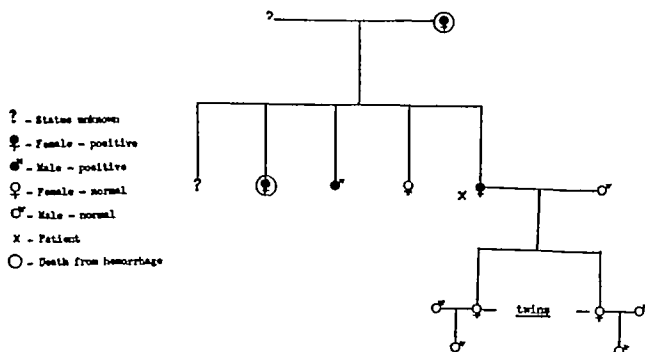


FIGURE 1

Infarction of the lungs is apt to occur when bed rest is abused following hemorrhage. The alterations of the blood due to the anemia may be a contributing factor to the phlebothrombosis. It is conceivable that the anemia and prolonged hemorrhage in an arteriosclerotic heart may initiate an acute coronary insufficiency.

The prognosis, in the absence of complications and provided hemorrhage can be controlled, is good so far as life is concerned. The severe and at times intractable hemorrhage, together with the anemia, often either makes semi-invalids of these patients or causes them to live restricted lives. Because of the repeated epistaxis, they pay numerous visits to the emergency wards of hospitals.

The treatment of familial hemorrhagic telangiectasia consists essentially of the control of epistaxis of varying degrees of severity. The multitude of agents and measures used in arresting the hemorrhage attests to failure to find a satisfactory method of managing the victims of this disorder. According to recent reports run, one of the newer therapeutic agents for decreasing capillary fragility, although not a specific, may be of some help in controlling the hemorrhagic tendency.<sup>18, 19</sup> Endocrine preparations, as mentioned above, have given indifferent

pressed by the results of this method of treatment. A measure of relief may be obtained by sclerosing of the vessels, but this requires a certain amount of skill that is outside the province of the average general practitioner. The fairly constant formation of new telangiectatic areas nullifies the effect of painstaking cauterization or sclerosis. Sooner or later one must rely on a tight vaseline-soaked gauze nasal pack. The patient complains of discomfort when this is inserted daily or every other day for weeks at a time, as is often necessary. The foul odor is obnoxious to the patient, to other members of the household and to the physician alike.

The case reported below illustrates the successful management of familial hemorrhagic telangiectasia and intractable epistaxis with a new hemostatic material, — oxidized cellulose gauze, — as described by Frantz and Lattes,<sup>20</sup> whose excellent article describes the preparation, action and uses of this latest addition to the list of hemostatic agents.

#### CASE REPORT

G. C., a 60-year-old housewife of Scottish English extraction, was admitted to the hospital because of severe nose bleeds. Since childhood she had had epistaxis, which had always been controlled by ice and light nasal packings until about 5 years before admission, when the hemorrhages occurred

more frequently and became severer. She had had many hospital admissions for arrest of the bleeding. Four years before admission she had been treated with radium. During the next 2 or 3 years the bleeding was less severe and occurred at longer intervals. For the greater part of the previous 10 months the patient had had a firm nasal packing of vaseline gauze inserted in the right nostril. The packing was removed and reinserted daily or on alternate days. On some occasions during this period she was able to go about her duties for several days without the packing. Usually, a sudden severe nosebleed, initiated by a cough or sneeze during an attack of asthma, necessitated emergency treatment and a return to the nasal pack. During such episodes it was not unusual for her to lose 400 to 800 cc of blood. At times she became so weak from hemorrhage that she was confined to bed for varying periods. While a patient at another hospital, she developed phlebotrombosis of both lower extremities and an infarct of the left lower lung. Bilateral superficial femoral-vein ligation was done, and she was discharged. She continued to have minor episodes of infarction after her return home.

The mother had died at the age of 52 of hemorrhage from the nose. A sister had died at 65 in a posthemorrhagic state following severe nasal bleeding. A brother, 63 years of age, had heart disease, and had had many hospital admissions, for nosebleeds. Three sons of this brother had reached adulthood without apparent bleeding. Another sister had died at the age of 21 of pneumonia following measles. A sister with hypertensive heart disease was living at the age of 68 and had no symptoms or signs of capillary hemorrhage. Each of twin daughters had a son, neither the daughters nor their sons showed telangiectases or any bleeding tendency.

The patient had had measles, mumps and whooping cough during childhood and for the past 20 years had had moderate to severe attacks of bronchial asthma. She had had three operations for frontal sinusitis about 30 years previously. At the age of 20, a bilateral oophorectomy had been performed. There were no symptoms referable to the gastrointestinal tract. The patient complained of slight exertional dyspnea and occasional attacks of pain across the upper chest. She had no genitourinary complaints and slept well when free from asthma and epistaxis. Menstruation had ceased following the operation 40 years previously.

Physical examination showed an obese woman who was bleeding rather profusely from the right nares through a firmly inserted nasal pack. Examination of the pharynx revealed postnasal hemorrhage. The nasal packing was removed, and a tight vaseline-soaked gauze tampon was inserted well into the cavity. The bleeding ceased, and the patient was given sedation and admitted to the hospital. The pulse was 92, and the blood pressure 60/50.

Examination of the blood disclosed a red-cell count of 3,700,000, with a hemoglobin of 69 per cent (9.9 gm Sahli), and a white-cell count of 6400, with 43 per cent neutrophils, 50 per cent lymphocytes, 1 per cent eosinophils and 6 per cent monocytes. The clotting time was 4 minutes, and the bleeding time 1 minute. The platelet count was 290,000. The prothrombin time of the patient and a control was 23 seconds. The hematocrit was 34, the specific gravity of whole blood 1.045, and the mean cell diameter of the red cells 7.7 cubic microns. There was beginning clot retraction in 15 minutes, with completion in 3 hours. The resistance of the red cells to hypotonic saline solution was normal. The patient was Type I AB, and Rh+. There was no indication of increased capillary fragility by the tourniquet test. A blood Hinton test was negative. The urine was essentially normal except that the sediment contained many white cells in an uncatheterized specimen. A chest film showed slight blunting of the right costophrenic angle indicative of an old pleurisy and some lateral protrusion of the lower left contour of the heart. An electrocardiogram showed small Q waves in Leads 1 and 2 and a low T wave in Lead 1. It was interpreted as being suggestive of myocardial damage.

Examination of the nose on the next day was unsatisfactory because of oozing, but a nose and throat consultant reported that the mucosa showed many telangiectatic areas and a moderate degree of atrophy. The telangiectases were more numerous and more marked on the right. A tiny, reddish-purple area was present on the tip of the tongue. A second lesion was seen on the ball of the index finger of the left hand. Several areas of telangiectases over the trunk, arms and

thighs, seen on previous examinations, had disappeared. On the fifth hospital day the blood pressure was 120/90 and the pulse 80.

The nasal pack was removed daily and reinserted. On the 7th hospital day it was not replaced, in spite of slight oozing. Since the patient had had two severe transfusion reactions during a previous admission to another hospital and because it was feared that an increase in blood volume might initiate hemorrhage, she was discharged 21 days after admission with a red-cell count of 3,300,000 and a hemoglobin of 62 per cent (8.9 gm Sahli).

Twenty-four days later she was readmitted with severe nasal hemorrhage. It was necessary to insert firm anterior and posterior nasal packs in the right nostril, as well as a light anterior pack in the left nostril. The patient was discharged on the following day with an anterior nasal pack of vaseline-soaked gauze. The red-cell count was 3,700,000, and the hemoglobin 58 per cent (8.3 gm Sahli). The hemorrhage was well controlled. Ten days later she was seen in the Emergency Room with severe epistaxis. At that time a firm tampon was inserted in the right nostril. This was changed on alternate days in her home.

The fourth admission for severe epistaxis took place 18 days following the last treatment in the Emergency Room. Oozing from the right nares had been continuous for 5 or 6 days in spite of a firmly inserted nasal tampon. The red-cell count was 3,700,000, and the hemoglobin 64 per cent (9.1 gm Sahli). The nasal packing was removed and reinserted. On the following day it was again removed. Bleeding had ceased, and it was not replaced. On the 3rd hospital day blood suddenly gushed from the right nostril following a cough, and the hemorrhage was controlled with difficulty. Several inches of oxidized cellulose gauze,\* which had been obtained from the manufacturer at the suggestion of Dr Roderick Macaulay, was inserted into the right nostril after the method of Houser.<sup>21</sup> After a lapse of 2 or 3 minutes the hemorrhage ceased. Two days later the resulting brittle material had been absorbed, and the bleeding began again. The nose was repacked, and the bleeding was almost immediately arrested. More of the material was used at this packing than previously. On the next day the gauze became granular and, within 24 hours, began to drop postnasally as tiny bits of a harmless gelatinous substance. Absorption and elimination were fairly complete in 7 days, and hemorrhage ensued. Prompt packing caused the bleeding to cease at once. The hemostatic material became loose in the nasal cavity and was removed 6 days after insertion. Inasmuch as epistaxis did not ensue, the pack was not reinserted. Eight days elapsed with only occasional episodes of minor oozing. This was readily controlled by the patient, but often stopped spontaneously. The patient was placed on 20 mg of rutin 3 times a day, the immediate members of her family were given instructions on the insertion of the oxidized cellulose gauze, and she was discharged on the 26th hospital day. On subsequent office visits the amount of rutin was increased to 40 mg 3 times a day. Because of nausea, it was necessary to reduce this dosage to a total daily maintenance dose of 100 mg. The hemorrhages, now easily controlled by oxidized cellulose gauze, have become less frequent and less severe since the institution of the rutin therapy. At present the patient is able to carry on all her normal activities, including household duties, with no difficulty.

## SUMMARY

The essential features of familial hemorrhagic telangiectasia (Rendu-Osler-Weber disease) are reviewed. The disease may be more closely related to other familial, hereditary hemorrhagic disorders than was formerly believed.

A case with intractable epistaxis is reported and discussed from the viewpoint of management with a new hemostatic product. Oxidized cellulose gauze should prove a useful addition to the therapeutic armamentarium for the control of epistaxis because

\*The material used was a 12-cm Hemo-Pak, manufactured by Johnson and Johnson, New Brunswick, New Jersey.

it is easily inserted, its hemostatic efficiency is high, it causes no discomfort to the patient, it is free from objectionable odor, and it is practically completely absorbed

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## RENAL INJURY FOLLOWING EXPOSURE TO CARBON TETRACHLORIDE\*

### Report of a Case

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MOST physicians associate carbon tetrachloride poisoning with serious liver damage and jaundice. This is not surprising, since knowledge of this substance stems from medical-school teaching, in which carbon tetrachloride was cited as an etiologic agent in toxic cirrhosis or acute atrophy of the liver and emphasis was placed on the risk of liver damage following the improper use of carbon tetrachloride as a vermifuge. The association of carbon tetrachloride with liver injury is also due in part to familiarity with its use as a hepatotoxic agent in animal experiments.<sup>1-3</sup> It is not generally recognized, however, that the inhalation of carbon tetrachloride by man frequently results in a clinical picture in which renal and pulmonary injury predominate and liver injury is not evident, although numerous authors have described such cases in more or less detail.<sup>4-10</sup> It appears that the syndrome of renal failure, accompanied by hypertension and severe azotemia induced by heavy exposure to carbon tetrachloride vapor, deserves additional emphasis in the general literature so that such cases may be recognized promptly and handled properly. The following case is therefore reported in detail.

G L, a 51 year-old Italian laborer employed in a large modern chemical plant in the Boston Metropolitan Area, was admitted to the hospital on June 14, 1946. He had been in good health all his life and was known to have had a normal blood pressure in 1945. According to his neighbors he drank wine fairly steadily but seldom became drunk. On May 28 he and six other laborers were assigned the job of cleaning

thick grease from the gears of a large mill prior to its being dismantled. They were at first given open buckets of naphtha and cloths with which to accomplish this task, but at 2:00 p.m. on May 29 the naphtha was replaced by carbon tetrachloride after an explosion meter test indicated the presence of an explosive concentration of naphtha about them. The seven men then worked with open buckets of carbon tetrachloride in which they soaked their rags to dissolve the thick grease. The work was carried on in a large, open room with 31 044 square feet of floor space and with adequate general but no local ventilation. The men were instructed to leave the vicinity of the work and get some fresh air for about 5 minutes every 1½ hour. Six of the men apparently did so to smoke. The patient, a non-smoker and an unusually conscientious worker, did not take these rest periods but continued to work steadily. All seven men worked at this job from 2:00 to 4:30 p.m. on May 29. The plant was closed the next day but on May 31 the same group worked from 8:00 a.m. to 4:30 p.m., except for a laborer who had been removed from the job about noon because he complained of "stomach ache and biliary vision" (This man's complaints cleared up on transfer to outdoor work and no subsequent illness developed.) On the following day the remaining six laborers again went to work with their buckets of carbon tetrachloride. The patient was removed from the job and assigned outdoor work about 2:00 p.m. after he had complained of dizziness and nausea. The remaining five men continued on the job which they completed without incident or illness toward the end of the following week.

The patient felt worse instead of better after his transfer to outdoor work, and was forced to leave the plant early because of nausea and abdominal discomfort. At home that evening the nausea increased and was accompanied by frequent emesis. He complained of generalized crampy abdominal pain and severe occipital headache. Several chills occurred, although no fever was noticed by his wife. That night the patient developed a dry, hacking nonproductive cough accompanied by pain in the lower chest and epigastrium. These complaints continued during the next 2 weeks during which there were frequent bouts of vertigo, chills, extreme anorexia and nausea as well as intermittent severe occipital headache. Vomiting occurred frequently and on one occasion bright red blood was noted in the vomitus. Considerable abdominal distention developed although the bowels moved daily, the

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stools being normal in color and consistence. On several occasions there were complaints of intermittent dimming of vision, described as being "like a cloud over the sun." Blood clots were expelled from the nose frequently, although no frank nosebleeds were noted. At no time were there any clinical signs of icterus or any evidence of bile in the urine.

The cause of the illness apparently was not clear during this period, although the exposure to carbon tetrachloride had been brought to the attention of the family physician by the plant nurse. Diagnostic x-ray examinations, including a gall-bladder series, gastrointestinal series and barium enema, were reported to be negative, although a small esophageal diverticulum was noted at the level of the seventh rib. The

patient remained restless and somewhat confused, and the nausea and headache continued during the first 3 hospital days. On the 4th day the patient began to feel better. The symptoms gradually lessened, and his condition slowly improved throughout the remainder of the hospital stay. On the 5th day, however, the temperature rose to 102°F and the cough increased, although the lungs remained clinically clear. Intramuscular injections of 30,000 units of penicillin every 2 hours were administered from the 5th through 9th hospital day. The administration of penicillin was accompanied by a rapid fall in temperature to normal, disappearance of the cough and clearing of the x-ray picture. The blood pressure, which had been markedly elevated on admission, fell slowly to al-

TABLE 1 Pertinent Data during Hospital Stay

DATE	BLOOD PRESSURE	BODY WEIGHT	BLOOD UREA NITROGEN	CHLORIDE	CARBON DIOXIDE	THYMOL TURBIDITY	BROM-SULFALEIN RETENTION (30 MIN)	PHENOL-SULFONE-PHTHALEIN EXCRETION (2 HR.)	UREA CLEARANCE
	mm Hg	kg	mg/100 cc	milliequiv/liter	milliequiv/liter	Maclagan units	%	%	%
6/14/46	210/100	—	118	92	17.6	—	31	—	—
6/15/46	172/70	64.2	115	86	15.4	5	—	—	—
6/16/46	150/82	64.8	71	86	16.5	—	—	—	—
6/17/46	158/82	65.8	62	92	17.3	—	—	—	—
6/18/46	158/100	62.6	112	94	17.0	2	31	40	26
6/19/46	160/88	61.0	80	93	16.3	—	—	—	—
6/20/46	168/98	58.6	76	99	20.0	2	—	—	—
6/21/46	164/115	59.0	57	106	20.2	—	—	—	—
6/22/46	170/104	58.2	40	107	19.6	—	—	35	—
6/23/46	168/98	58.0	—	—	—	—	—	—	—
6/24/46	164/100	57.6	34	114	17.6	—	—	—	—
6/25/46	160/100	57.8	33	103	18.0	—	—	—	—
6/26/46	144/80	57.2	35	110	18.7	—	—	—	—
6/27/46	110/70	57.0	—	—	—	—	—	—	—
6/28/46	144/80	57.6	29	102	23.4	1	36	—	34
6/29/46	138/92	57.2	—	—	—	—	—	55	—
6/30/46	150/96	58.0	—	—	—	—	—	—	—
7/1/46	138/96	57.4	18	96	22.0	—	—	—	—
7/2/46	140/84	58.0	—	—	—	—	—	—	—
7/3/46	138/94	58.0	—	—	—	—	—	—	—

patient was referred to the hospital when his condition was becoming progressively worse, with increasing anorexia, vomiting, abdominal discomfort and lethargy.

Physical examination revealed a lethargic, somnolent, acutely ill patient. The breath was foul. No jaundice, cyanosis or petechiae were noted. The conjunctivas were pale, and the mucous membranes of the mouth were studded with purpuric spots. Examination of the chest revealed diminished expansion, but the lungs were clear throughout. The heart was slightly enlarged to the left, and the rate was regular and rapid, with a Grade I systolic murmur at the apex. The abdomen was soft and nontender. No organs or masses were palpable, and liver dullness was normal in extent. There was no evidence of free peritoneal fluid. The remainder of the physical examination was not remarkable.

The temperature was 98°F, the pulse 90, and the respirations 36. The blood pressure was 210/100.

Examination of the blood at the time of admission disclosed a hemoglobin of 15.1 gm and a white-cell count of 11,500, with a fairly normal differential. The platelets appeared normal. The urine had a specific gravity of 1.010 and gave a + test for protein, and the sediment contained 40 to 50 red cells per high-power field. A rare cellular cast was noted. Blood chemical studies revealed the presence of a fairly severe nitrogen retention and moderate acidosis. The total protein, calcium, phosphorus and alkaline phosphatase were normal.

X-ray examination of the chest on the day after admission revealed a diffuse granular increase in the markings in both lung bases, most marked on the left, where there was a small amount of fluid in the costophrenic angle. These findings were interpreted as suggesting a resolving pneumonia at the bases. The x-ray film also disclosed slight cardiac enlargement. An electrocardiogram was normal.

The patient was given intravenous infusions of glucose, physiologic saline solution and sodium bicarbonate, as well as 10 gm of methionine by mouth, and 5 cc of crude liver extract intramuscularly each day. Lumbar puncture on the 2nd hospital day revealed no abnormalities. The patient re-

mained normal levels at the time of discharge. The blood urea nitrogen, blood pressure and other blood chemical changes during the hospital stay are presented in Table 1.

While the patient was in the hospital, special tests of liver and kidney function were performed. The thymol turbidity was never elevated above normal, although it dropped from a level of 5 Maclagan units<sup>11</sup> following admission to 1 unit at the time of discharge. The bromsulfalein test indicated a persistent increase in dye retention, but no elevation in serum bilirubin was present at any time. The urea clearance and phenolsulfonephthalein excretion were impaired throughout the hospital stay.

The patient was discharged from the hospital 20 days after admission. At that time he appeared well but still complained of frequent occipital headaches and generalized weakness. Six weeks after the exposure to carbon tetrachloride, he felt perfectly well and was able to return to work. At that time physical examination was not remarkable, and the liver and spleen were not palpable. The blood pressure was 136/82, and the nonprotein nitrogen 33 mg per 100 cc.

This case illustrates several points in connection with poisoning following relatively brief exposure to carbon tetrachloride that deserve emphasis. The absence of any fire or explosion hazard has endowed carbon tetrachloride with a reputation as a safe solvent for general use that it does not deserve. In this case, carbon tetrachloride was substituted for naphtha to eliminate the explosion hazard accompanying the use of the inflammable solvent. It should have been evident that a toxic concentration of carbon tetrachloride would be encountered, since the explosion-meter test disclosed an explosive con-

centration of naphtha (this would be at least 1 per cent), and carbon tetrachloride is even more volatile. It is surprising that all the workers were not affected, for serious or even fatal poisoning may follow exposure to 0.1 to 0.5 per cent carbon tetrachloride.<sup>12</sup> There was undoubtedly considerable variation in the concentration actually breathed, however, — the explosive naphtha concentrations were encountered near the buckets rather than at head level. Unfortunately, no carbon tetrachloride concentrations were determined.

Marked variation in susceptibility to poisoning by carbon tetrachloride has previously been noted.<sup>12-13</sup> It is interesting that only two men of the seven exposed were affected and that only one was made seriously ill. It is quite possible, however, that careful examination and testing of the remaining men would have disclosed some evidences of kidney or liver injury.

It is impossible to state whether the therapy that the patient received after reaching the hospital had any pronounced effect on the course of the disease despite the diuresis and fall in blood urea nitrogen observed, since diuresis may be expected at about this time in the natural course of the disease. It appears probable, however, that the administration of fluids and electrolytes was helpful in promoting a return of kidney function. The effect of methionine on the clinical course is not clear, its action in protecting the livers of protein-depleted dogs from injury from chlorinated hydrocarbons has been amply demonstrated.<sup>14-15</sup> Shaffer, Carpenter and Moses<sup>4</sup> have shown, however, that methionine is ineffective in preventing or correcting liver damage from carbon tetrachloride in dogs with an adequate protein reserve. The fact that the patient had eaten relatively little for the two weeks prior to admission made it appear desirable to give him an adequate protein intake. It was considered necessary, however, to maintain the protein intake at a relatively low level, adequate calories being supplied in the form of carbohydrate, to avoid an excessive accumulation of nitrogenous waste products in the body, and methionine was supplied in an effort to mitigate the undesirable effects on the already damaged liver of further protein depletion. Therapy in this case was directed primarily at the kidneys, since regeneration of the liver proceeds rapidly following acute poisoning by carbon tetrachloride and since liver damage in this case was not at any time sufficiently severe to cause clinical icterus. Conservative measures were adequate.

The multiplicity of action of carbon tetrachloride is well illustrated by this case. Definite evidences of pulmonary irritation and impaired liver function were noted, and the history suggested that gastrointestinal involvement was present during the first

week of the illness. Reports in the literature indicate that carbon tetrachloride poisoning is characterized by pulmonary involvement<sup>6</sup> or acute abdominal symptoms,<sup>16</sup> as well as the more frequent renal or liver injury. Recently, carbon tetrachloride has been reported to induce the development of duodenal ulcer.<sup>17</sup>

### SUMMARY

The generally accepted but erroneous belief that acute carbon tetrachloride poisoning is usually associated with severe liver injury may lead to failure to establish a correct diagnosis in cases of carbon tetrachloride poisoning resulting from inhalation of its vapors.

A case of severe renal injury without clinical evidence of liver injury following brief but intense exposure to carbon tetrachloride vapor is presented in detail.

The clinical picture in this case was dominated by anorexia, lethargy, hypertension, azotemia and urinary findings suggestive of nephritis. Complete recovery, with a return of the blood pressure to normal, and disappearance of evidences of renal disease took place under conservative therapy.

The possibility that this syndrome occurs frequently following the inhalation of carbon tetrachloride is emphasized.

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## THE DETECTION OF TUBERCLE BACILLI BY FLUORESCENCE MICROSCOPY

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THE method of fluorescent staining for the demonstration of tubercle bacilli in smears proposed in 1937 by Hagemann<sup>1</sup> offered a promising simplification of the rather cumbersome Ziehl-Neelsen technic. Many in this country have tried the procedure and have not been impressed with the results.<sup>2</sup> The objections are in some cases due to insufficient trial and in others to inadequate equipment. Better methods have now been developed, and it is the purpose of this paper to outline the technic and equipment and the results obtained therewith.

The tubercle bacillus does not fluoresce of its own accord but can be made to do so by staining with a fluorescent dye. Auramine O, readily available from several supply houses, was used in the studies described below. A saturated aqueous solution of this dye is filtered to remove the surplus undissolved particles. The filtrate is unstable but will retain its staining power as long as two weeks if kept in the refrigerator. Thinly spread, heat-fixed smears on new glass slides are stained for two minutes with this auramine solution at room temperature without the troublesome steaming required by the Ziehl-Neelsen method. The slides are then washed in water, decolorized with acid alcohol and again washed with water. They are then counterstained with a 1:1000 aqueous solution of potassium permanganate for thirty seconds, as recommended by Lee,<sup>3</sup> washed with water and allowed to dry in the air. The whole procedure requires only about three and a half minutes.

Light sources originally supplied for the purpose are not adequate. The present studies were done with a home-made lamp and filter described by Graham.<sup>4, 5</sup> The materials cost less than ten dollars. The essential parts are a 500-watt motion-picture projector bulb in a sheet metal housing, which also holds two 7.5-cm double condensing lenses. It is necessary to delete from the lamp beam all but the blue light, this may be accomplished by the use of a liquid filter made as follows. An excess of ammonium hydroxide is added to a saturated aqueous solution of copper sulfate, this is placed in a rectangular museum jar and is diluted with water until the correct shade is obtained to give the results described below.

The wave length of the exciting and emitted light is further narrowed by placing in the ocular lens of the microscope a yellow glass filter equivalent to a Wratten K-2. This and the proper dilution of

the aqueous filter will give a Nile-green background. This background for the microscopical field is chosen in preference to the black background usually advised. Against a green color, nonfluorescent elements on the slide are readily seen, and the focus can be maintained throughout the search for fluorescent particles. The green color minimizes eyestrain, to which some workers have objected. Another objection has been that a dark room is needed for examination of fluorescent-stained smears. When the green background is used it is only necessary to reduce the light in the examining room somewhat—for example, by drawing the shades nearest the microscope. We have found this most suitable for general use. Any standard monocular microscope with a 10x ocular and with 10x and 43x objectives may be used. No special quartz lenses are necessary. Nearly all oil-immersion lenses fluoresce and cannot be employed. The intensity of the fluorescence of the bacilli is not enough to allow the use of a binocular microscope.

The slides are first examined under low power and are searched systematically for yellow specks. The bacilli will, of course, be extremely small under this magnification, appearing only as minute rod-shaped flecks of yellow in the green field. They are, however, easily seen, and after a short period of practice, it is possible to search an entire slide under the low power in less than twenty minutes. As in the Ziehl-Neelsen stain, there are acid-fast fluorescent artifacts, thus, confirmation under higher power is necessary. With the high-dry lens it is possible to identify the tubercle bacillus more closely. It appears as a long, thin, irregularly stained rod that is pale whitish yellow. The bacillus usually has a slightly irregular outline.

Smears from a wide variety of sources have been examined by this method. These include exudates and caseous material from pleural cavities, meninges, bone and tendon sheaths, as well as sputum and gastric lavages. With few exceptions smears from these locations showed few artifacts, and these were easily differentiated from tubercle bacilli. Smears made from lymph nodes may be unsatisfactory because of the large number of artifacts. In sputum the number of artifacts is occasionally large enough to interfere with examination of the smear. Thus, in the hands of an inexperienced examiner, false positive reactions may be reported. In the examination of seventy-six sputum specimens from healthy medical students, only two were found with so many artifacts that examination of the slide was unsatisfactory.

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In a series of 15 color-blind medical students, 10 found more tubercle bacilli in the examination of positive smears stained with the fluorescent method than they did in smears stained with the Ziehl-Neelsen technic.

Richards<sup>6</sup> reports that when the two stains are used in sequence on the same areas of the slide, more organisms appear with the fluorescent than with the Ziehl-Neelsen method

### SUMMARY

The advantages of the fluorescent staining of the tubercle bacillus over the Ziehl-Neelsen technic are many. It requires only about three and a half minutes to stain a slide completely without the use of heat. Because of the use of lenses of lower power it is possible to examine a smear completely in less than twenty minutes — a point that has been made by Lind and Shaughnessy.<sup>7</sup> This method is considered more accurate than the Ziehl-Neelsen

technic. The technic can be used safely for the screening of large numbers of sputums, the Ziehl-Neelsen method being restricted to the few specimens in which questionable fluorescent particles are encountered. Color-blind persons can identify the tubercle bacillus more readily with the fluorescent than with the Ziehl-Neelsen

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## MEDICAL PROGRESS

### WAR WOUNDS OF THE ABDOMEN (Concluded)

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**Liver** The liver is frequently involved in abdominal wounds, and almost always in right thoraco-abdominal wounds. Consequently, x-ray films often show shell fragments within the liver shadow. Since these foreign bodies are well tolerated and their removal difficult, they are usually left in situ. This led to rather conservative therapy of liver wounds early in the war. It soon became evident that a more radical technic was required and that adequate drainage was necessary to avoid bile peritonitis, bile empyema or subdiaphragmatic abscesses. Although Betts<sup>27</sup> believes that a wound produced by a fragment 3 mm. or less in diameter, may be treated conservatively, the usual opinion is that any penetrating wound of the liver demands exploration, suture of any laceration of the diaphragm and the establishment of adequate subcostal drainage. This is due to the fact that the tiniest fragment may injure a large biliary radical.

The other major problem in the initial surgery of liver wounds is the control of hemorrhage. In the 829 patients studied by Madding, Lawrence and Kennedy,<sup>2, 28</sup> spontaneous hemostasis had occurred at the time of operation in 91 per cent. Various methods have been employed to control active bleeding. Fibrin foam or a hemostatic gelatin sponge should be ideal but was not available for this purpose. Large, deep sutures through the liver are often effective, but their use is hazardous,

because they may initiate even more profuse bleeding. A tag of omentum may be placed in the defect. A detached portion of the rectus muscle may be of help. Large gauze packs have not been too satisfactory. They do not act as an adequate drain and, if left in place too long, form a large cavity that is slow to obliterate.

Madding advises the use of temporary gauze packs or a Penrose drain with gauze laid against the oozing surface. The drain should be started on the fourth or fifth day, and completely withdrawn by the tenth to the twelfth day. In only 1 case was grave postoperative hemorrhage encountered. Wounds near the hilus were most serious because of the proximity of other vital structures.

**Gall bladder and bile ducts** These injuries are rare, and are nearly always associated with wounds of other viscera. Depending on the severity of the wound, an injured gall bladder may be treated either by suture and cholecystostomy or by cholecystectomy. Damaged ducts should be repaired. A successful two-stage repair was described by Park.<sup>29</sup>

**Spleen** In World War I wounds of the spleen were treated by packing, with the result that mortality was high. Splenectomy was often performed, but the mortality was 100 per cent. In World War II the consensus was that splenectomy should be done whenever any treatment is warranted. The most interesting trend in the performance of splenectomy has been the widespread use of the transthoracic approach. Poole<sup>3</sup> found that the

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mortality in 159 cases removed by the trans-abdominal route was 29.5 per cent. The mortality in 171 cases of transthoracic splenectomy was 19.8 per cent. A transthoracic approach for strictly abdominal wounds, however, should not be made because of the possibility of fecal contamination of the pleura.

**Kidneys** Wounds of the kidneys are treated either by packing or by nephrectomy. A conservative attitude is adopted whenever possible, nephrectomy being retained for severe damage to the vessels at the pedicle or to the renal pelvis, or for complete fragmentation of the organ. In the Second Auxiliary Surgical Group nephrectomy was required in 28.1 per cent of all cases, gauze packs were not favored. Postoperatively, urinary drainage generally continues for several days. A persistent urinary fistula, secondary hemorrhage and sepsis furnish the usual postoperative complications.

**Ureter** In any wound in which it may have been damaged it is necessary to expose the ureter, since overlooked wounds lead to death from urinary extravasation. Tiny wounds can be sutured. High transections may be treated by a telescoping anastomosis. If the transection is low, the ureter may be reimplanted in the bladder. Kimbrough<sup>30</sup> advises suture of the injured ureter over a catheter and proximal diversion of the urinary stream.

**Bladder** All patients suspected of bladder wounds should be catheterized preoperatively. Kimbrough<sup>30</sup> stresses the diagnostic value of this procedure and also advises digital rectal examination with the catheter in place.

Wounds are treated by suture and by suprapubic cystotomy. Urethral catheter drainage is not sufficient in itself to assure an empty bladder, and therefore must not be used to the exclusion of a suprapubic tube. It is also necessary to provide adequate drainage to the space of Retzius. The bladder is rarely involved alone, so that a careful search should be made for other visceral damage. Thus, Michels,<sup>2</sup> in 155 cases, found bowel damage in 88 per cent. There were no deaths when only the bladder was involved, and only 1 patient developed perivesicular infection.

**Prostate and urethra** The value of primary repair of the membranous or prostatic urethra has been emphasized by Leadbetter.<sup>31</sup> He has described a method that can be carried out entirely through a suprapubic approach, and has obtained healing without stricture. The essentials of his technic comprise the passage of a urethral catheter, the accurate visual repair of the urethra, when possible, through the floor of the bladder and the anchoring of the dislocated prostate to its normal position in the perineum by deep stay sutures.

If this procedure cannot be carried out as a primary measure, a suprapubic cystotomy may be done, to be followed in a few days by a urethral repair. The importance of early repair is shown by

the statistics of Conger,<sup>32</sup> who observed severe, non-dilatable strictures in cases that were repaired six weeks after injury, whereas in those done soon after wounding the patients did well.

**Pancreas** Wounds of the pancreas carry a high mortality chiefly because other viscera are injured at the same time. The usual treatment has been to establish drainage with a Penrose wick. The development of acute pancreatitis or skin irritation at the site of the drain frequently occurs if the patient survives.

### *Major Vascular Wounds*

Patients with wounds of the aorta do not live to reach the surgical hospital. On the other hand, major wounds of the vena cava and the iliac, portal or superior mesenteric veins may be found on the operating table. These patients, according to Jarvis, Byers and Platt<sup>14</sup> show a characteristic clinical syndrome. Response to shock therapy is slight, but it is usually possible to raise the systolic pressure to 50 or 60. The pressure falls to 0 as soon as the peritoneal cavity is opened, and remains at that level until the bleeding is stopped.

If the wound can be controlled rapidly the patient may survive. Suture of a tangential wound or ligation of the vessel may be done. Packs or tangential clamps have been used in desperate cases, but are not recommended. Suture involves a greater hazard because of the possibility of embolism, so that ligation is preferred.

In 75 cases of major vascular injury observed at the Second Auxiliary Surgical Group the mortality was 73 per cent. No patient in the 8 cases in which the vena cava was ligated or sutured above the renal vessels survived. The major causes of death were hemorrhage (27 cases), anuria (12 cases) and pulmonary emboli (4 cases).

Swingle and Flynn,<sup>2</sup> discussing retroperitoneal hematomas, state that "the real significance [of such a hematoma] other than for the clinical signs which are indistinguishable from those of a viscus perforation lies in the fact that it may obscure injury to vital retroperitoneal structures." Therefore, if the position of the hematoma could indicate possible injury to the ureter, posterior aspect of colon, rectum, duodenum or bladder, these areas should be explored. Churchill<sup>33</sup> has pointed out that retroperitoneal hemorrhage is not a hazard per se unless the hemorrhage continues. In such an event the bleeding must be controlled.

### *Closure of the Incision*

Insecure abdominal closure will lead to a high incidence of wound dehiscence, whereas if the closure is carried out by ordinary civilian methods there will be many serious infections. Thus, Jarvis, Byers and Platt<sup>14</sup> found that in the first 28 abdominal cases done by their surgical team there was dehiscence in 6 cases. Thereafter, they changed the

method of closure in a radical fashion, and in the next 100 cases had no disruptions. They recommended the following method. The peritoneum is closed with a running catgut suture. The posterior and anterior rectus sheaths are then closed with interrupted nonabsorbable sutures. This is further reinforced by numerous through-and-through sutures placed about 2 cm lateral to the incision and about 1 cm apart. A strip of vaseline-soaked gauze is placed between the skin edges down to the fascia. This gauze is removed in forty-eight hours. This same method is recommended by Churchill,<sup>22</sup> and others.

Certain methods of wound management were abandoned as experience increased. Laparotomies conducted through wounds of entrance and exit were found to be generally unsatisfactory. When colostomies were brought out through the main incision, the problems of infection and dehiscence were enhanced.

When a large part of the abdominal wall has been destroyed, tight closure will be impossible. Ogilvie<sup>24</sup> recommends the suture of a strip of vaseline-soaked canvas over the exposed bowel. This can be removed when granulations have formed over the bowel, and the hernia treated subsequently.

### *Evisceration*

Patients with evisceration show an unusual degree of shock, and have a poor prognosis. Bradford, Battle and Pasachoff<sup>25</sup> found a mortality of 76.9 per cent in their cases with evisceration (omental eviscerations were not included). Childs<sup>26</sup> found a 10 per cent incidence of evisceration in a series of 3154 cases of abdominal and thoracoabdominal wounds. The small bowel, omentum and colon were the usual organs involved, comprising 87 per cent of the group. The evisceration occurred more frequently at the wound of exit. The over-all mortality was 40.3 per cent — nearly twice as high as that in corresponding wounds without evisceration. If the colon alone had protruded the mortality was 57.5 per cent, and if the omentum alone, 37.2 per cent.

### *Thoracoabdominal Wounds*

A full discussion of this subject is beyond the scope of this paper, but several important features of this group of wounds must be mentioned. Excellent analyses have been presented by Snyder,<sup>27</sup> DeBakey,<sup>28</sup> Wylie et al.<sup>29</sup> and Mason and Imes.<sup>30</sup> Shorter series are described by Welch and Tuhy,<sup>31</sup> Sanger<sup>32</sup> and Tuttle.<sup>33</sup> The features are as follows: any wound in which the diaphragm may have been traversed must be explored, with few exceptions, surgery of chest wounds should be done first in multiple wounds, thoracoabdominal wounds and combined intrathoracic and abdominal wounds, most thoracoabdominal wounds are best handled first by the thoracic approach, a celiotomy being performed only if the abdominal wounds cannot be

cared for by the transdiaphragmatic route (the relative advantages of the various types of abdominal and thoracic incisions are described by Betts<sup>34</sup>), the incision, which should usually be made through the ninth and tenth rib bed or interspace, may be extended 2.5 to 5 cm on to the abdominal wall if necessary<sup>37</sup> — and small accessory muscle-splitting incisions may be made for subdiaphragmatic drainage or extentionization of colon, but extension onto the abdominal wall is not approved by some authorities, because the wound may break down<sup>37, 38</sup>, and the diaphragm must be sutured with non-absorbable material, preferably in two layers.

A summary of the experience of the Second Auxiliary Surgical Group is presented in an excellent article by Wylie et al.<sup>29</sup> In 3532 patients with abdominal wounds, 25.5 per cent of cases were thoracoabdominal. The missiles had entered the abdomen from the thorax in 837 cases, and from the opposite direction in only 66. The right and left sides were equally involved. The authors discuss preoperative and postoperative treatment in detail, stressing the importance of accurate x-ray examination, the use of intercostal novocain block and postoperative bronchoscopic aspiration.

With right-sided wounds the liver was involved in 407 of 435 cases, followed in order, by the kidney, colon, stomach, small bowel, duodenum and gall bladder. On the left side, in 448 cases, the spleen was injured in 272, the stomach in 167, and the colon in 145. The liver, left kidney, small intestine and pancreas were involved with diminishing frequency. In 362 cases the whole operative procedure was carried out through the chest.

Mortality rates decreased progressively from 36.7 per cent in 1943 to 20 per cent in 1945. Wounds of five or more organs were uniformly fatal. In 234 fatal cases, the cause of death was shock in 130, peritonitis in 20, pneumonia in 17, renal failure in 15 and pulmonary emboli in 10.

### *Blast Injuries*

Blast injuries of the abdomen were relatively infrequent in land warfare. Underwater explosions provided many small groups of cases that have been reported by various authors.

The mechanism of blast injury has been investigated by Greaves et al.<sup>34</sup> and by Webster and his associates.<sup>35</sup> They found that solid viscera are rarely affected. If the intestine is full of fluid it is also relatively immune, but if gas is present, there will be damage. Lesions were never found in animals in which the gastrointestinal tract was empty. Two types of lesion are found in fatal cases: complete perforation of the wall and hemorrhagic discoloration of the wall.

A typical sequence of symptoms is described by Webster et al.<sup>35</sup> as follows: a sensation of a tremendous blow on the abdomen at the time of the explosion, profuse vomiting, often of blood, bloody

diarrhea, severe abdominal pain, fever, the temperature averaging 102°F, rigidity of the abdominal wall at one time or another, a white-cell count of 11,000 to 30,000, prolonged elevation of the sedimentation rate, and weight loss

Operation is indicated for frank perforations soon after injury, for late perforations following hemorrhagic infarction and for drainage of abscesses.<sup>46</sup> The decision is often difficult because of associated pulmonary damage. It must be made within twelve hours, however, and doubtful cases explored.<sup>46</sup> In 7 cases operated on by Goligher, King and Simmons,<sup>47</sup> twenty perforations were found in each case, ranging from 1.0 to 3.7 cm in diameter. The mortality in all cases is about 25 per cent.

*Postoperative care* Essential features of the postoperative care include replacement and maintenance of a normal blood volume, with constant check by copper sulfate studies of the hematocrit and serum protein — if blood volume determinations are available they will be of great value, the intravenous administration of adequate amounts of fluid, sugar, salt and, if available, protein, continuous nasogastric suction, not by means of Miller-Abbott tubes, which, in general, are too complicated for field use, but by a Levin tube, which is as effective if it is introduced before operation and maintained, accurate observation of the urine, special attention to the lungs to prevent pneumonia — intercostal block, tracheal or bronchoscopic aspiration may be necessary, chemotherapy, and gradual restoration of food intake as improvement occurs. It is of extreme importance that these cases are non-transportable for a period of ten to twelve days.

### REPARATIVE SURGERY

This secondary surgery is performed in large hospitals in the Zone of Communications. In the Army general hospitals overseas the care of abdominal wounds was resolved into the following main categories: the management of colostomies, the drainage of residual abscesses and the care of septic wounds, and the treatment of intestinal obstruction. These topics are discussed below in order.

#### *Management of Colostomies*

Colcock<sup>21</sup> has stated that few colostomy patients escape without some complication, such as wound infection, wound separation, retraction of the colostomy, evisceration or the development of abdominal-wall, intra-abdominal, subphrenic or retroperitoneal abscesses. He suggests that practically all could be avoided by adequate mobilization of the colon. I have seen complete dissolution of the incision when the wound of entrance has been used as the exploratory incision and the colostomy brought out through it, serious abscesses after colostomy have been performed distal to the perforation and intra-peritoneal retraction of the sigmoid colostomy when mobilization has not been sufficient. With increasing

experience, these errors in initial surgery became less numerous.

Horsley and Michaux<sup>48</sup> observed the results in 111 cases in a general hospital in Italy, in which the colostomy closed in 40 cases and in which new colostomies were required in 5 because of the complications listed above. Whether or not a colostomy was to be closed was dictated to some extent by transportation facilities. The general rule was to evacuate the patient to the Zone of the Interior for closure if he was debilitated or had other severe injuries. If closure was to be done, the usual time was six weeks after injury. The procedure should not be attempted in the presence of wound sepsis or if peritonitis has existed within six to eight weeks, nor should it be done until all plastic surgery on the lower bowel, anal sphincter, urinary bladder or perineum has been completed.

It was found that a few minor perforations can be closed and the loop exteriorized — the perforations will heal, and the loop will then retract within the peritoneal cavity. Since all types of colostomies tend to retract, a glass rod should always be used with loop colostomies, and the bowel should be opened in the long axis on the oral side of the rod.

There was no mortality following closure, and fecal drainage occurred in only 1 case. The bowel could usually be closed with transverse sutures. In a few cases resection and end-to-end anastomosis were necessary. The bowel was always placed within the peritoneal cavity.

Gregg and Moseley<sup>49</sup> believe that digital examinations of the stoma will determine the best type of repair. With a loop colostomy, pressure with the finger will invaginate the posterior wall of the bowel into the peritoneal cavity. To close it, the colostomy is freed and turned in with two layers of transverse sutures. If a long, thin spur is present, it can be cut with crushing clamps. Closure is effected in the same fashion after tension on the bowel has been relieved by partial opening of the peritoneum. A thick spur indicates either a mesenteric artery from a rotated loop of colon or a loop of small bowel. In this event the peritoneum must be opened widely. If there is a constricted or retracted colostomy, plastic repair is done at the site of the stricture, which is opened longitudinally and closed transversely. The authors fear resection with end-to-end anastomosis — an apprehension that is unfounded in view of later reports.

#### *Drainage of Residual Abscesses and Care of Septic Wounds*

Wound care does not differ from that encountered in civilian practice. A conservative attitude may properly be taken so far as residual abscesses are concerned. Ogilvie<sup>34, 50-52</sup> has observed that practically all except subphrenic and pelvic abscesses tend to burrow to the surface, discharging spontaneously through the wound or incision. In my experience

many cases of subdiaphragmatic infections have subsided under adequate chemotherapy, and operation need not be considered urgent unless an undrained collection of bile is suspected. Pelvic abscesses can be drained easily through the rectum as soon as they become fluctuant. It is not advisable to wait for spontaneous rupture, since this may be delayed for a long period.

### *Treatment of Intestinal Obstruction*

Obstruction of the small bowel is frequent after war wounds, probably because of the extreme trauma, hemorrhage and infection. This complication may appear at any time in the early convalescence or thereafter. Conservative therapy is unlikely to be successful except soon after the initial laparotomy, when the adhesions are still of a plastic type. Later, laparotomy will be necessary. Many adhesions are usually found, and it is generally unwise to attempt to free them all, only the obstruction can be relieved in most cases.<sup>42</sup> Enterostomy may be necessary if the lumen of the bowel has been compromised by previous obstruction.

The late care of thoracoabdominal wounds in an overseas general hospital was discussed by Fox.<sup>44</sup> Of 270 patients only 43 per cent required further operations, 36 per cent secondary closure of wounds, 11 per cent thoracotomy for empyema, 5.2 per cent exploration of the subphrenic region, 4.4 per cent colostomy closure and 1.8 per cent decortication. The mortality was 2.6 per cent. Complications consisted chiefly of empyema and subphrenic abscesses.

### RECONSTRUCTIVE SURGERY

Reconstructive surgery is performed in the hospitals of the Zone of the Interior. As in the overseas general hospitals the main problem is that of colostomy closure. In addition, wounds of the rectum are closed, incisional hernias are repaired, urethral strictures may need operative intervention, occasional cases of intestinal obstruction require operation, and some foreign bodies are removed.

### *Colostomy Closure*

Many papers have appeared on the subject of colostomy closures. At present all the cases in which closure has been done in the general hospitals of the Army are being collected by Poer<sup>45</sup> and will be published shortly. It is his impression that intraperitoneal end-to-end anastomosis should be performed. He has found a high degree of immunity to infection in these patients and has been unable to prove that preoperative or postoperative chemotherapy has improved the results. There were only 17 deaths in over 2000 cases.

Several other surgeons have presented smaller series but have reached essentially the same conclusions. Roettig, Glasser and Barney<sup>46</sup> advise the

intraperitoneal closure because there may be unpleasant sensations when the bowel is incarcerated on straining or defecation, because ventral hernia is frequent after extraperitoneal closure, and because an extraperitoneal closure offers a good site for internal herniation and strangulation of small bowel. Foisie<sup>47</sup> also advocates an intraperitoneal closure. He was able to prepare most of his cases by crushing the spur.

Keene<sup>48</sup> notes that if two colonic stomas are in such proximity that the same dressing covers both, feces will progress from one to the other. He states that a patient with a colostomy invariably builds up a fecal impaction in the distal loop while being evacuated to the United States. He believes that resection and open end-to-end anastomosis are so satisfactory that, when a proximal colostomy is made for a wound in the distal colon, the colon should be completely transected and the two stomas placed at least 6 cm apart.

Saunders and Halperin<sup>49</sup> list the most frequent problems encountered in colostomy closure as subcutaneous herniation of the bowel, complete absence of a spur, interposed foreign bowel or mesentery between colostomy limbs, varying degrees of rotation of limbs, secondary perforation or fistulas, inflammatory or granulomatous masses and musculo-fascial defects in the abdominal wall. They believe that the anatomic repair of these defects requires an intraperitoneal operation. They favor and describe the Pauchet closure.

Hamilton<sup>50</sup> found that extraperitoneal closure was associated with a much higher incidence of complications than intraperitoneal. Recurrent fecal fistula and intestinal obstruction were frequent after extraperitoneal closures.

Advocates of extraperitoneal closures include Pilcher and Nadeau.<sup>51</sup> Shallow, Eger and Tourish,<sup>52</sup> from civilian experience, have described a method of closure that falls in the same group.

A critical survey of these various reports suggests the following conclusions. After proper preparation, the mortality following any type of closure is extremely low. Plastic and extraperitoneal closures occasionally develop temporary fecal fistulas or intestinal obstruction. Postoperative barium enemas will demonstrate a surprising amount of stenosis in many cases, even though the patients are clinically free of symptoms. The complications can be avoided by resection of the involved bowel, an open end-to-end anastomosis and secondary closure of the abdominal wound. This is therefore the preferable method.

In colostomy closure various other problems arise. One of the most important is the selection of the proper time for operation. All agree that the other operative procedures in the pelvis must first be completed, and that the patient must be in a good state of nutrition. Preferably, he should be within 10 pounds of his normal weight.

The exact method of preparation of the bowel for closure has varied considerably. Usually, meticulous mechanical cleansing of the bowel was associated with several days of preoperative chemotherapy in the form of sulfasuxidine, sulfathalidine or sulfaguanidine. Preoperative barium studies of all the distal and proximal bowel, as well as x-ray visualization of any fistulas present, are important.

### *Closure of Rectal Wounds*

Hamilton,<sup>61</sup> describing the operative technic, states that these wounds are serious, because there is usually much scar tissue in the rectal wall and often a stricture or abscess as well. A completely defunctioning colostomy is essential. A generous incision should be made with removal of the coccyx and the fifth and fourth sacral segments if necessary. The rectal wall must be freed widely. Stenosis may be corrected by a longitudinal incision with transverse closure well away from the fistula. The fistula should be closed with two or three layers of sutures. Any associated foreign body that contributes to persistent sepsis is removed. The incision is allowed to heal by granulation.

Roettig, Glasser and Barney<sup>66</sup> state there are three important steps in closure of rectal perforations: adequate exposure, with removal of the coccyx and as much of the sacrum as necessary, as wide mobilization of the rectum as possible, both laterally and in front of the sacrum, and interposition of some fat or muscle tissue between the portion of the rectum containing transverse closure and the sacrum before the skin is closed. The wound is closed without drainage.

### *Laceration of Anal Sphincter*

In such cases a colostomy is essential, according to Roettig, Glasser and Barney.<sup>66</sup> The sphincter is mobilized through a semicircular incision 3 cm from the mucocutaneous margin. If closure is still impossible, the defect should be reduced as much as feasible. A second stage is carried out several weeks later after sphincter-control exercises and daily dilatation. Sphincter action and control must be tested before the colostomy is closed.

### *Intestinal Obstruction*

Barney, Roettig and Jones<sup>64</sup> observed that in the last year in the Rhoads General Hospital, mechanical obstruction was found in a ratio of 1:18.5 cases. The incidence in the small bowel was three and a half times that in the large bowel. In the former all types of obstruction were found, whereas in the colon the most frequent cause was a small lumen following colostomy closure.

In the experience of these authors the incidence of strangulation of the small intestine or marked interference with blood supply was far greater in war wounds than the usual 10 per cent figure in civilian practice. They therefore advocate early laparotomy

rather than the use of the Miller-Abbott tube. If the obstruction is in the colon, an attempt is made to delay operation long enough to give the patient an adequate amount of the sulfonamides. Thereafter, a resection and end-to-end anastomosis are done.

### *Removal of Foreign Bodies*

Intraperitoneal foreign bodies are preferably removed at the time of initial surgery. Large shell fragments that have not been recovered may be removed in the Zone of the Interior. Those that contribute to persistent fecal or urinary fistulas, osteomyelitis or continued purulent discharge from a wound must be taken out. In addition, many that are in close relation to large vessels or to the hollow viscera should be removed. Those buried in the retroperitoneal musculature and in the liver usually produce no symptoms and may be left in place.

### *Repair of Hernia*

No special problems are presented except that fascial repairs of hernias are frequently necessary.

### *Late Urinary Problems*

Kimbrough<sup>20</sup> found that of the urogenital injuries seen in the general hospitals in this country, the kidneys had been wounded in 14.0 per cent, the ureter in 3.4 per cent, the bladder in 14.5 per cent, and the external genitalia in 68.1 per cent of patients. Nephrectomy had been performed in only 2.4 per cent of patients with kidney wounds. Prather<sup>65</sup> observed that nephrectomy was necessary in 2 of 3 cases of ureteral fistula evacuated to the Zone of the Interior.

The importance of early repair of the urethra<sup>27</sup> and the difficulty attending late attempts have been stressed by Conger.<sup>32</sup> Stricture is frequent after late repair, and dilatation is often impossible.

Rectovesicocutaneous fistulas are the most difficult late sequelae of bladder wounds to treat. Roettig, Glasser and Barney<sup>66</sup> state that the fistulas usually heal spontaneously if colostomy, suprapubic cystostomy and inlying urethral catheters are used.

Cystitis and epididymitis were also found to be frequent complications after bladder wounds.

\* \* \*

In conclusion it might be appropriate to list several of the unsolved problems of abdominal surgery in warfare. The first and the most important is an accurate appraisal of the role of chemotherapy, both in the prophylaxis and in the treatment of peritonitis and other types of sepsis.

The prophylaxis of peritonitis has not yet been possible. Early in the war many soldiers took sulfonamide tablets by mouth immediately after they were wounded. It is obvious that the sulfonamides were useless in this fashion. The introduction

of streptomycin and of the relatively nonabsorbable sulfonamides, sulfasuxidine and sulfathaladine, however, offers a method to reduce significantly the number of virulent organisms in the gastrointestinal tract. It may be possible to develop a technic for the oral administration of these drugs for a few days before battle that would be valuable.

So far as the therapeutic administration of the sulfonamides and penicillin is concerned, it is impossible to assess their value satisfactorily. The variability of the types of wounds, the absence of any adequate control series and the omission of details of therapy in many records indicate that opinions rather than facts have been recorded. Furthermore, compared with the dosage that is employed today, penicillin was not available in sufficient quantities to influence the course of an established peritonitis.

Lyons<sup>46, 47</sup> emphasized the fact that adequate excision of devitalized tissue is much more important than the bacterial flora of the wound. He further stated as follows:

Sulfonamide therapy has been shown to be adequate for the wound in danger only of hemolytic streptococci. Penicillin is the drug of choice for all other wounds subject to invasive infections. No virtue is attached to combinations of penicillin and a sulfonamide compound as the treatment of infected wounds.

He concludes that local chemotherapy is unnecessary and undesirable and that penicillin administered parenterally is the chemotherapeutic agent of choice.

Imes,<sup>48</sup> discussing traumatic surgery of the abdomen, believed that the sulfonamides and penicillin were about equally effective in the treatment and prevention of peritonitis and that there was little doubt that chemotherapy played a significant role in the lower incidence of peritoneal infections following abdominal injuries. Drye<sup>2</sup> agreed that penicillin and the sulfonamides were important, but found it impossible to assess them accurately. He considered the mortality significantly lower, however, in the series treated with penicillin than in that in which sulfonamides were employed.

A second problem is concerned with the resuscitation of the wounded. Why is it that many patients, especially those with abdominal wounds, cannot be brought out of shock? Despite blood replacement and adequate surgery the blood pressure remains low, and death occurs in twenty-four to forty-eight hours. It is generally believed that overwhelming infection is present, but further clarification is needed.

A third problem is that of the so-called "multiplicity factor." Why is it that a man with five wounds of the small intestine has an excellent chance of survival, whereas a single wound of five viscera is almost uniformly fatal?

Moreover, the technical management of wounds of the colon demands further consideration. When one realizes that practically all the abdominal surgery

in general hospitals in the Zone of the Interior is concerned with the management of colostomies, it can be appreciated that any safe method whereby the convalescent period could be shortened would be of value. Thus, Imes<sup>49</sup> has observed that "the contention of those who hold that all wounds of the colon should be exteriorized because of its poor healing tendency and greater than apparent tissue damage from shell fragments is not supported by our experience." In particular, then, is there a place for primary closure of wounds of the colon, or is this such an unsafe procedure in the hands of the ordinary surgeon that it should not be countenanced? Also, what is the best method of management of severe wounds of the right portion of the colon?

Finally, in common with other extensive wounds, what is the explanation of postoperative renal failure? This is one of the most important causes of death in patients who survive the period of shock.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 33321

#### PRESENTATION OF CASE

**First admission** A twenty-nine-year-old Jewish housewife was admitted to the hospital because of diarrhea

The patient's illness dated from an automobile accident nine years previously, which was followed by a nervous breakdown At that time she was supposed to have had a spine injury, which required six months' treatment, and during the convalescence she developed diarrhea (six to fifteen movements a day), which continued more or less constantly until admission to the hospital There was no blood or mucus but merely watery diarrhea Treatment by many physicians in several parts of the country gave no relief, and four years before entry she was explored at an outside hospital Dilated portions of small bowel, which were about the size of the large

bowel, with other areas of constriction and marked thickening of the wall, were noted There was marked fusion of the mesenteric lymph nodes, with the formation of large masses The mesentery was extremely friable and bled readily The diagnosis was thought to be tuberculosis of the small bowel extending from the ligament of Treitz to within 75 cm of the ileocecal valve The patient improved markedly following laparotomy, and three weeks later she had the first formed stool in a year She spent about six months in Arizona, felt much better and gained about 30 pounds Two years later, however, the diarrhea and emotional upsets returned, and the following year she was studied at another hospital, where tuberculosis was supposedly ruled out by x-ray examination and skin tests A diagnosis of ileitis was made at that time She continued to have six to fifteen movements a day, remained somewhat high-strung, tired easily, and lost about 20 pounds

Physical examination revealed a small, thin, poorly nourished woman with a high diaphragm and tympany over the normal liver dullness On the left side of the abdomen a large mass was palpated and percussed 8 cm below the costal margin No shifting dullness or other evidence of fluid was found The abdomen was slightly distended and felt doughy

The examination of the blood and urine was negative The stools were liquid and guaiac negative A barium enema required nearly three times the usual quantity for filling The colon was grossly

dilated and atonic. The ileum would not fill. There was slight deformity in the region of the ileocecal valve, but the mucosa was apparently intact. The hepatic flexure rose unusually high, whereas the splenic flexure was displaced downward, the entire abdomen appeared more dense than usual, possibly due to ascites. There were no gas-filled loops of small bowel. A gastrointestinal series revealed the stomach to be markedly displaced to the right and upward, there was a definite delay in emptying of the jejunum, with marked distortion. There was one long loop on the left side, about twice the normal size, that remained filled until the six-hour examination. After four hours the terminal ileum was fairly well filled and appeared small and slightly irregular, with the patient upright, fluid levels formed in the dilated small bowel but no gas was present. Examination of the chest was negative except for the unusually high diaphragm. She was discharged on the fourth day.

*Second admission* (one and a half years later). The patient was fairly well until seven months before entry, when she developed vomiting attacks that increased in severity. There appeared to be no exciting cause, and at the time of admission they were occurring every forty-eight to seventy-two hours, always preceded by nausea and occurring during the day. Despite this she had gained weight and felt much better than she had two years previously.

Physical examination revealed clubbing of the fingers and a doughy, tender abdomen. The spleen was palpable two fingerbreadths below the left costal margin.

Routine examination data were negative, and a barium enema revealed a deformity of the ileocecal valve and a dilated terminal ileum. On the second day a laparotomy was performed. At the operation a loop of small bowel was found glued to the abdominal wall, the intestine was greatly thickened, as was the mesentery of the small bowel, which was quite firm. There was interadherence of loops of small bowel and the mesenteries, and an enormous loop of jejunum could be elevated into the wound. A short circuit was performed between the distended, thickened jejunum and a piece of comparatively healthy, normal-sized small bowel. It was estimated, however, that at least half the small bowel was involved and possibly more. Areas of bowel that were obviously previously diseased could be seen in all quadrants of the abdomen. A biopsy of jejunum showed chronic inflammatory changes of a non-specific nature.

The patient improved and was discharged about one month after admission.

*Third admission* (six and a half years later). The patient returned for evaluation of a therapeutic abortion. She was two and a half months pregnant. Because the patient was free from symptoms, abortion was not performed.

*Fourth admission* (three years later). The patient had been delivered of an infant by cesarean section two and a half years previously and subsequently developed sudden marked abdominal distention, with rupture of the operative sutures. Following this the distention subsided spontaneously. Two and a half months before admission she had noted that her abdomen seemed unusually swollen, and it had remained so. There were no other symptoms.

Physical examination revealed only slight distention and tenderness of the upper abdomen and pitting edema of the lower edge, more so on the left, than on the right, with slight tenderness on the left.

Laboratory data, including total protein and nonprotein nitrogen levels, Congo red test and prothrombin time, were negative. A cephalin flocculation test was + in twenty-four hours and ++ in forty-eight hours. X-ray studies revealed clear lung fields and a high diaphragm, especially on the left. The heart and mediastinum showed a slight shift to the right. Diaphragmatic motion was active and equal. There was a gas bubble between the anterior portion of the right leaf of the diaphragm and the liver, with a fluid level beneath it, which was interpreted as bowel between the liver and diaphragm. The upper half of the abdomen showed a homogeneous increased density that extended below the right iliac crest and was inseparable from the liver shadow. A plain film of the abdomen failed to show bowel in the upper right abdomen and midabdomen, but no definite liver shadow was seen. Upright films confirmed the presence of an air bubble in a confined area beneath the right leaf of the diaphragm, possibly air in an unusually high stomach.

Some observers thought they could feel a rather soft, possibly cystic mass in the upper abdomen, which on one occasion was said to be ballotable to the left flank from the right upper quadrant.

A gastrointestinal series and barium enema one week after admission revealed the stomach to be markedly displaced to the right and slightly forward by a large mass occupying the left upper quadrant. The mass appeared somewhat lobulated. In addition the stomach displaced the duodenum and small intestine downward. There was a small area of radiolucency, resembling fat, within the mass. A normal spleen was not visualized as in the previous films. The liver was small. A barium enema revealed an extrinsic soft-tissue mass displacing the transverse colon from above and posteriorly.

An exploration was done on the sixteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR ALFRED KRANES. The remission of symptoms following a simple exploratory laparotomy seems extraordinary and raises considerable doubt regarding the diagnosis of tuberculosis of the small bowel.

As you might well imagine, this has been for me an extremely confusing problem and on first reading over the abstract I was completely bewildered. As I went over it more carefully it seemed to me that the patient's illness might be divided into two phases. The first, beginning at the age of twenty and ending at thirty, following the enterojejunostomy for obstruction, was characterized by symptoms resulting from the diseased small bowel. The second phase dated from thirty to the time of admission, when she was forty. According to the record, during the last ten years she was completely asymptomatic. Is that a fair assumption to make?

DR DANIEL S ELLIS Yes, after the operation at this hospital she was in perfectly good health.

DR KRANES We have therefore to consider two questions. What was the nature of the small-bowel lesion that caused the original symptoms? Secondly, what was the nature of this mass in the left upper quadrant that brought her to the hospital at the age of forty? Is it fair to ask whether this patient survived the operation or came to autopsy? The reason I ask, is that time is short and I do not want to waste too much time on the small-bowel lesion.

DR TRACY B MALLORY She survived the operation.

DR KRANES If that is the case, it leads me to believe that they do not know any more about the disease in the small bowel than has already been described in the previous operative note and in the record. If that assumption is correct, I can probably speak freely about the probable nature of the small-bowel disease. It seems to me that the likeliest explanation for all the small-bowel symptoms is the diagnosis that was subsequently made, namely, regional enteritis. That diagnosis explains the history of this patient's illness and the x-ray findings, as well as the operative findings, more satisfactorily than anything else I can think of. The one thing that disturbs me greatly about the history of this illness is the fact that no pain was mentioned during the early part of the disease. That is unusual in any extensive lesion of the small bowel. Is it true that this patient never had any pain?

DR ALLEN She had pain associated with nausea and vomiting before the first operation, the one done at another hospital.

DR KRANES The original description of the bowel, as well as that of the mesentery and the large lymph nodes, is quite characteristic of regional enteritis, particularly the enlarged nodes. Some surgeons advocate removal of such lymph nodes, since it has been claimed that they are the reservoir of residual infection and predispose to recurrence. The disease has been experimentally produced, or a reasonable facsimile of it, by injecting sclerosing substances into the mesenteric lymphatic vessels. The histologic picture in animals is almost indistinguishable from that in human cases. Furthermore, the operative findings at the second lapa-

rotomy are quite in keeping with the diagnosis of regional enteritis. It is characteristic for inflammatory changes to be produced between loops of bowel and for fistulous tracts to form eventually. There were none in this patient. There is nothing in the history or symptoms or operative findings that contradicts the diagnosis of regional enteritis.

So far as tuberculosis goes, I think that is most unlikely, since ulcerative tuberculosis of the small bowel is usually a terminal event in advanced pulmonary tuberculosis. I also believe that the course of the disease is strongly against tuberculosis.

I shall leave that for a moment and go on to the mass in the left upper quadrant. What was its nature? I am afraid that I shall need quite a bit of help from the X-ray Department. I must confess that this description is exceedingly confusing. There seems to be an implication of two masses, one on the right side that extends to the right iliac region without any evidence of bowel in that region, and another on the left side. I was allowed to look at these films yesterday.

DR RICHARD SCHATZKI I shall show you the outline of this mass, there was only one.

DR KRANES The other thing that confuses me is the statement that a normal spleen was not visualized, as in the previous films. That to me is an important statement, because if a normal spleen was visualized on previous films, the diagnosis that has occurred to me must be completely discarded.

DR ELLIS There is only one mention of the spleen in all the films taken over a period of fifteen years.

DR SCHATZKI No shadow of the spleen was visualized, unless one calls this peculiar mass the spleen.

DR ELLIS In the original examination Dr Holmes described the spleen, which I am sure is the same mass that subsequently increased in size.

DR SCHATZKI The original film was taken in 1936, and the mass at that time displaced the stomach to the right. In the next ten years it became eight times as large, displacing the stomach to the right and slightly forward and the colon downward.

DR KRANES How about the small bowel?

DR SCHATZKI There is nothing that can be added to the report.

DR KRANES This mass is much larger than it was originally. What interests me is why it was not found at exploration. The operative note said nothing regarding it. I should have expected that a mass of that size would have been described, but perhaps the emergency of the intestinal obstruction and the extensive disease in the small bowel prevented extensive exploration within the abdomen.

Dr Schatzki, was this mass separate from the left kidney?

DR SCHATZKI Yes.

Dr KRANES In other words, it was a gradually increasing epigastric mass, probably chiefly in the left upper quadrant, completely asymptomatic and unattached to the stomach, to the kidney and probably to the adrenal gland. That leaves us little else to consider.

One point to be decided is whether or not this mass was in any way related to the previous disease of the small bowel. It is difficult for me to connect the small bowel disease with the mass. Although it is true that regional enteritis not infrequently perforates and produces localized abscesses, it is impossible for me to believe that an abscess of this size could have been present for ten years without discomfort, fever or something in the way of symptoms. Furthermore, it is a most unusual site for an abscess. Finally, abscesses rarely attain the size described here. So I think I shall discard any relation between this mass and the previous small-bowel disease.

When one has multiple lesions and extensive disease within the abdomen, particularly a large mass in the left upper quadrant, the possibility of lymphoma comes to mind. Could the small-bowel disease have been lymphoma, and could the remissions have been due to the number of x-ray examinations she had had for many years? I hardly think that diagnostic x-ray doses could have produced this type of remission. The finding of large mesenteric nodes at the first operation is rather suggestive, but if she did have lymphoma, she must have cured herself spontaneously and I do not believe one can consider it seriously.

The next question to decide is whether the mass was solid or cystic. It seems to me that solid masses in this area and of this duration should have caused more in the way of symptoms. Furthermore, a large solid mass in this region should have been readily palpable. I am much more in favor of a cystic mass. The only cystic mass with which I am familiar in the left upper quadrant is a cyst of the spleen. That is the first thing that occurred to me, but as I studied the case more carefully, I hesitated to suggest it as a possibility because the condition is so rare. Yet I can think of no other explanation that fits all the findings in this case any better than a large cyst of the spleen. Actually, this patient had the proper background for such a diagnosis. Most of the cases described, of which there are not many, occurred in young women, and this started before the age of twenty-nine. A large proportion of them have a history of preceding trauma, which was present here. Most of these cysts, if that is what this is, contain old, brown, coagulated fluid, probably the result of the original hematoma.

In thinking of cystic diseases in this area, one also has to consider a dermoid cyst. They are extremely rare in the left upper quadrant, although

a few have been reported. What about the area of radiolucency? Is that striking?

Dr SCHATZKI No, not at all. I should not consider it definite.

Dr KRANES Other conditions to be mentioned, of course, are retroperitoneal sarcoma and fibroma. It seems to me that any malignant tumor in this area is ruled out by the duration of the disease. The most probable diagnosis, so far as I am concerned, is a large splenic cyst, the result of old trauma.

Dr EDWARD B. BENEDICT I should think that this might well have been a pancreatic cyst.

Dr KRANES That is a perfectly good suggestion. A large cyst in the tail of the pancreas can produce exactly the same picture, and I certainly should have mentioned it, but I see no way of differentiating a splenic and a pancreatic cyst clinically, except that the patient was a woman and had had an injury, two factors more in keeping with splenic cyst than with pancreatic cyst.

Dr ELLIS This patient came in with a purely mechanical problem. She felt perfectly well and had had no bowel symptoms for many years. At first, of course, we tried to tie this mass in the abdomen with the previous disease, but we could not do it in any way that seemed reasonable. Therefore, it boiled down to the fact that she had a mass in the abdomen. What was it? In addition to the conditions mentioned by Dr Kranes we thought of amyloid disease. Was this a huge amyloid spleen or liver? There was no positive evidence of amyloid disease in the laboratory tests. We were left with the diagnosis of cyst for the reasons that Dr Kranes has mentioned. The pre-operative diagnosis was cyst of the spleen, pancreas or mesentery, with betting on every one.

#### CLINICAL DIAGNOSIS

Cyst of spleen, pancreas or mesentery

#### Dr KRANES'S DIAGNOSIS

Cyst of spleen

#### ANATOMICAL DIAGNOSIS

Cyst of pancreas

#### PATHOLOGICAL DISCUSSION

Dr MALLORY Dr Allen, will you discuss the operative findings?

Dr ARTHUR W. ALLEN Dr Kranes has discussed the problem presented at the time of this woman's first admission, when she had the short-circuiting procedure, extremely well, and he arrived at as nearly a correct diagnosis as we could obtain from the exploratory operation. We short-circuited the obstructed loop of small intestine, and the pathological diagnosis that was made on the specimen was a nonspecific granulomatous lesion involving the small bowel — Crohn's disease or regional enteritis. She had had a peritonitis preceding or following the first exploration, so at the time of the

short-circuiting procedure it was difficult to re-explore extensively. She was not in good condition, and although we made some effort to discover the mass that had been described in the left upper quadrant, we could not get to it without too much dissection. So we short-circuited the loop, believing that that was all we should do.

She came back the last time with a perfectly huge mass, which could be felt on the left side. It was not hard but felt like a soft cyst. It was an interesting problem, and the various possibilities of cystic mass in this location were, of course, considered. All have been named that we did consider, but in going over the films with Dr. Schatzki I finally decided on the diagnosis of a cyst of the spleen. Cysts of the spleen always occur at a pole, and one had to assume that it was the lower pole of the spleen from which this mass had developed. The reason that it did not extend farther downward was that she had had peritonitis and the adhesions had kept it confined in that direction. It had followed the line of least resistance to fill the whole upper abdomen.

At operation we found that the mass was cystic, as expected, but that it arose from the pancreas. After determining that, we drained the cyst of 5 liters of fluid by suction, incised it and then anastomosed it to a loop of jejunum high up, just beyond the ligament of Treitz, the only piece of normal intestine that we could find nearby.

DR. MALLORY: This operation was essentially an internal marsupialization of the cyst.

DR. ALLEN: We had two choices. The other was to bring the edges of the cyst out through the abdominal wall, hoping that the sinus might eventually close, as they often do, if the sinus did not close, one could then implant the sinus into the intestine. The intestines were so interadherent, with every loop stuck to another, that it was not pleasant to think of having to go back into the abdomen again to implant a sinus tract. Within the last year or two Dr. Ralph Adams,\* of the Lahey Clinic, has reported the anastomosis of pancreatic cysts to the small intestine, associated with an enteroenterostomy. We should have liked to do an enteroenterostomy here but could not do it. All we could do was to make an anastomosis to the jejunum. We took out a generous portion of the cyst wall for pathological examination.

DR. MALLORY: A section of the cyst wall showed it to be lined by columnar epithelium, similar in appearance to the lining of the normal pancreatic ducts. This was surrounded by dense fibrous tissue, and in the periphery there were numerous atrophic clusters of pancreatic acini. So we felt quite certain that Dr. Allen was correct in assuming that it had originated in the pancreas.

## CASE 33322

### PRESENTATION OF CASE

A forty-year-old housewife entered the hospital because of right chest pain and hemoptyses.

Thirteen years before entry she developed an upper respiratory infection followed by cough, fever and pleuritic pain on the right side. An x-ray film of the chest was said to have shown fluid at the right base. A sputum smear was negative for acid-fast organisms. After several weeks in bed she felt completely well except for a persistent, mild, slightly productive cough, which became accentuated when she had a "cold." Eight years before entry two pregnancies were interrupted on the basis of another chest x-ray film. Four and a half years before entry she began to have hemoptyses. X-ray films at that time revealed no abnormality and sputum examination was negative. Several months later she was admitted to a tuberculosis sanatorium, where x-ray examination revealed a shift of mediastinal contents to the right and considerable soft infiltration in the lower half of the right lung field. One sputum was reported positive, but ten succeeding examinations over the remaining seventeen months' stay at the sanatorium were negative. A right pneumothorax was performed, and this was maintained after discharge for a total of twenty-three months because of continued hemoptyses. Two years before entry she was admitted to another tuberculosis sanatorium, where bronchoscopy revealed that the right main bronchus was practically occluded just below the carina by a whitish tumor, which bled profusely on touching. A biopsy specimen was said to show undifferentiated or small-cell carcinoma. Bronchoscopic electrocoagulation of this tumor was carried out six times, and the patient received several courses of deep x-ray therapy. The hemoptyses, however, still continued. The patient also complained of right anterior chest pain, which was often severe enough to require codein for relief. Exertional dyspnea, easy fatigue, chronic cough and pallor had been present for several years.

On physical examination the patient was pale but appeared to be in no acute distress. The trachea was deviated to the right. The entire right lung field was dull to percussion. Over the upper portion there was bronchial breathing and tactile fremitus was increased. Over the lower portion, the breath sounds were absent and tactile fremitus was decreased. The heart was shifted to the right. There was a Grade II systolic murmur at the apex. The abdomen and extremities were normal.

The temperature was 98.6°F, the pulse 90, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

Examination of the blood showed a red-cell count of 2,500,000 with 6.0 gm of hemoglobin, and

\*Adams, R., and Nishijima, R. A. Surgical treatment of pancreatic cysts. *Surg., Gynec. & Obst.* 83: 181-187, 1946.

a white-cell count of 3500, with 75 per cent neutrophils. The urine was normal.

An x-ray film showed the right chest cavity to be smaller than the left. The mediastinum was retracted to the right. The right lung was completely airless except for a small bubble in the right upper chest. The left lung was clear.

Bronchoscopy on the third hospital day was unsuccessful because of profuse hemorrhage. On the sixth hospital day another attempt at bronchoscopy was made. Again there was profuse bronchial hemorrhage, and the patient died suddenly in respiratory failure.

### DIFFERENTIAL DIAGNOSIS

DR CARROLL B. MILLER: I shall depart from the usual procedure in these case discussions and declare at the start that there can be little doubt that the diagnosis in this case is adenoma of the right main bronchus. I shall then discuss why other diagnoses are unnecessary and unlikely. That there may be other conditions associated with the adenoma warrants mention and deserves consideration, but they would be secondary and probably not necessarily related to the adenoma.

The age of the patient, the sex and the events in the thirteen-year-history of respiratory symptoms indicative of bronchial obstruction and associated collapse, pneumonitis and possibly bronchiectasis all point to an adenoma. Such a tumor has characteristically a long history, and thus, by virtue of its being admittedly a "benign tumor," does not cause progressive systemic decimating effects as are seen in a malignant tumor of the bronchus. Parenthetically, however, if the side effects of retained infection and pulmonary destruction occur in association with an adenoma or if the adenoma undergoes malignant degeneration as it is often claimed, the picture may be indistinguishable from that of a primary bronchiogenic carcinoma.

Three interesting details in the history must be discussed: the suspicion of tuberculosis, the biopsy report after bronchoscopy of carcinoma and the lack of response to x-ray therapy. It is not uncommon for a patient with any lung disease to be suspected of having tuberculous infection, and rightly so. Indeed, this patient's lung may well have shown tuberculosis at post-mortem examination, but that is not an important feature of the case. Hemoptysis, pleural effusion and x-ray signs of a soft infiltration in the right lower lung field are enough to make any diagnostician highly suspicious of tuberculosis, but sputum examinations, with one exception, were repeatedly negative for acid-fast organisms, and when bronchoscopy was finally resorted to, an obstructing tumor was found. The effect of this tumor in the main bronchus was sufficient to account for collapse, pneumonitis, pleural effusion and shift of the mediastinum—in

short, the picture that the patient showed on various occasions.

The microscopical diagnosis on biopsy two years previously was "undifferentiated carcinoma," and the tumor failed to respond to x-ray treatment. Without much doubt an undifferentiated carcinoma, thus probably highly malignant, would neither have permitted the patient to live two years nor have failed to show some response to radiation therapy. To quote Boyd's *Surgical Pathology*, "Surface cells [of these adenomas] may undergo squamous metaplasia which may suggest epidermoid carcinoma." Similarly, the nature and arrangement of the cells have sometimes provoked the diagnosis of "alveolar sarcoma, basal cell carcinoma or adenocarcinoma."

Let us consider the physical examination and roentgenologic picture of the patient. She had signs of extensive collapse of the right lung. Laboratory data indicated a probably chronic secondary anemia and tendency toward agranulocytosis, the results of chronic infection.

Taken all together, the history, physical findings, laboratory data, x-ray findings and bronchoscopic reports strongly suggest a benign, massively obstructing tumor of the right main bronchus, and this must have been a bronchial adenoma. Other lesions, such as a nonspecific granuloma, a foreign-body granuloma (the history is negative for aspiration) or a gumma (there is no Hinton report, and I assume that the serologic reaction of the serum was negative), may be dismissed as extremely rare and unlikely. The tumor, unfortunately, was malignant for this patient, since it was responsible for her demise, because of its extreme vascularity, hemorrhages were frequent, as is often the case with adenomas, and the cause of death was undoubtedly an inundation of the left bronchial tree, with consequent suffocation. It is this type of case that makes the surgeon so frequently prefer to proceed with lung resection without the benefit of cytologic examination of the neoplasm, once the gross appearance and site of obstruction have been determined by bronchoscopy.

No discussion of the pathology and surgical treatment of bronchial adenoma is complete without mention of the frequent, almost invariable, dumb-bell shape of the tumor, which characteristic justifies the abandonment of treatment by bronchoscopic morcellation and the adoption of resection at the site of that portion of the lung containing and blocked off by the tumor.

### CLINICAL DIAGNOSIS

Bronchial tumor, type undetermined, with recurrent hemorrhages

### DR. MILLER'S DIAGNOSES

Adenoma of right main bronchus, with bronchiectasis

Hemorrhage into left bronchial system

## ANATOMICAL DIAGNOSIS

*Bronchial adenoma of right main bronchus, with hemorrhage into left lung*

## PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN As Dr Miller predicted, this patient had a bronchial adenoma. The lumen of the right main bronchus was completely occluded by a pinkish gray tumor (Fig 1). The

The left lung was fluffy, and the bronchi and alveoli were filled with blood — an obvious aspiration of blood from the tumor.

Microscopically the tumor was a typical adenoma, with no evidence of carcinoma. The regional lymph nodes showed chronic inflammation.

Have you any comment, Dr Benedict?

DR EDWARD B BENEDICT The danger of serious hemorrhage from bronchial adenoma is a real one.

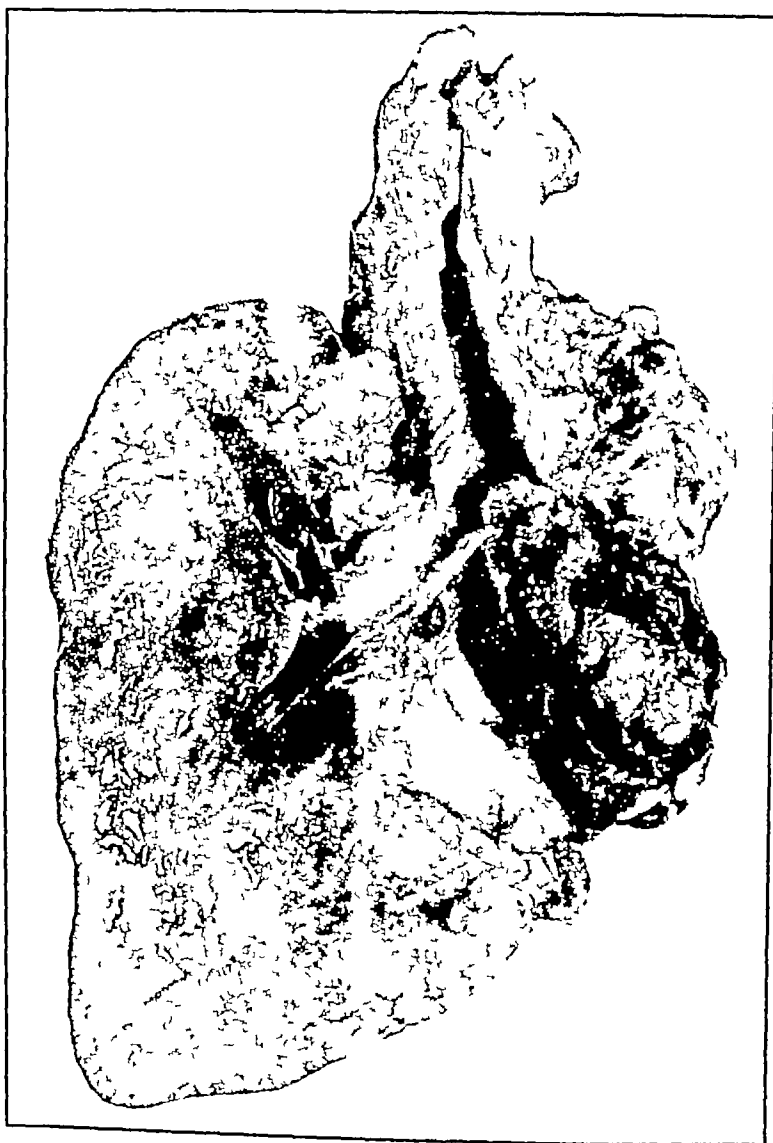


FIGURE 1

tumor was attached to the bronchial wall at a point approximately 1.5 cm from the bifurcation of the trachea and had grown proximally for a short distance into the trachea and distally into the secondary bronchi to form a large mass 9.5 cm long and 6.0 cm in diameter. Nowhere was the bronchial wall destroyed; the tumor merely grew down the lumens in pseudopod formation. Beyond the tumor there was bronchiectasis in the small collapsed lung.

If an adenoma completely blocks one main bronchus it means, of course, that the patient has only one useful lung. If serious hemorrhage occurs, either spontaneously or at the time of a bronchoscopy biopsy, it may mean drowning of the good lung by hemorrhage and a rapidly fatal termination. The experienced bronchoscopist can usually differentiate adenoma from carcinoma by the gross appearance. The former presents a smooth rounded surface

whereas the latter usually is nodular and irregular. On the other hand, there have been at least two cases of carcinoma in my experience in which a rather smooth polypoid finger-like carcinoma extended upward along the main bronchus, grossly simulating an adenoma. If the bronchoscopist is suspicious of adenoma from a long history of intermittent attacks of bronchial obstruction with repeated hemoptyses and so-called "pneumonia" and if, in addition, he finds a smooth grossly benign-appearing tumor blocking one main bronchus, he might do well to take no biopsy for fear of serious hemorrhage. The surgeon would then probably operate on the basis of the history, the x-ray examination, the gross findings at bronchoscopy and the probability of irreparable lung damage. The bron-

choscopist will have done his part by indicating the gross appearance of the tumor and the level at which it appears in the bronchus.

In the case under discussion, although the gross appearance of the tumor was that of a benign adenoma, there had been a previous report of carcinoma. The taking of a biopsy in this particular case, therefore, seemed especially important. Moreover, the tumor's position in this case, lying across the carina, made it somewhat inaccessible to surgical approach. Although many adenomas have been safely biopsied at bronchoscopy and even largely removed bronchoscopically, in retrospect one cannot help wondering what the outcome would have been if a pneumonectomy had been attempted without bronchoscopic biopsy.



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## WALTER PRENTICE BOWERS

Walter Prentice Bowers, of whose death on July 22 we are all aware, may well be ranked as the departed dean of the Massachusetts medical profession.

A life-long general practitioner of medicine and honored by Harvard University as such, a former president of the Massachusetts Medical Society and managing editor of the *Journal* for fifteen years, he was a man of stature among us.

To his older colleagues in the Society, he was a thoughtful, kindly friend; to many more, a wise counselor, to the youngest, we trust, an inspiring legend. Like Dr. Samuel Johnson,

he kept his friendships in repair, and his benign presence at all except the more recent Council meetings belied his ninety-odd years.

"Know ye not," said David to his servants, "that there is \* \* \* a great man fallen this day \* \* \* ?"

## RESEARCH ON THE COMMON COLD

FOR several years prior to the discovery of the virus of influenza there was considerable interest in the etiology of the common cold. A number of important investigations were reported during that time, particularly by Dochez and his co-workers,<sup>1,2</sup> in New York City and by Long and his collaborators<sup>3</sup> in Baltimore. These studies were necessarily limited in scope and rather laborious, chiefly because of the failure to find a suitable experimental animal that is susceptible to the disease. To be sure, the chimpanzee was found to be susceptible, but that animal is difficult to handle and not readily available in adequate numbers. The use of human volunteers likewise seemed to entail so many difficulties that only a few investigations involving transmission to human subjects were reported. Some success was claimed with cultivation of a virus from the common cold and its propagation in tissue culture,<sup>4</sup> but this was not confirmed by other workers. Meanwhile, the ease with which the viruses of influenza are isolated and manipulated has diverted the attention of many workers to studies with these agents, and a vast amount of information concerning influenzal infections has accumulated.

The recent war stimulated interest in a number of other human diseases that were of major importance and required immediate investigation. Researches on some of these diseases were also hampered by the failure to find suitable experimental animals. Under the impetus of the war, however, it was possible to obtain both funds and human volunteers to carry out fairly elaborate studies on the etiology and transmission of such diseases as infectious hepatitis and primary atypical pneumonia and on the therapeutic efficacy of certain chemical agents in human malaria. In this

country conscientious objectors and inmates of prisons were the main source of such volunteers. The feasibility of using human volunteers rekindled interest in the simple respiratory infections, particularly since the risks involved in acquiring such infections are much less than those that accompany experimental infections with the diseases just mentioned. At least three groups of workers have engaged in such studies on the common cold, and preliminary reports of the results of the work of two of these groups are now available.

Abernethy,<sup>5</sup> of the Commission on Acute Respiratory Diseases, last year reported briefly on the successful transmission of minor respiratory illnesses to a group of human volunteers. He used filtered secretions from two patients who had different types of illness. The first had an incubation period of one or two days and was characterized chiefly by sneezing, nasal obstruction, coryza and cough, in the other, the incubation period was five or six days, sore throat was an outstanding feature, and nasal symptoms were minimal. These infections reproduced the same type of symptoms on transfer of filtered secretions to other volunteers in each instance. There appeared to be no cross immunity, and whereas a partial immunity to the homologous filtrate was demonstrated to the disease having the longer incubation period, no such immunity resulted from the illness with the short incubation period and the predominantly catarrhal symptoms. No illness resulted from inoculation of control filtrates obtained from the subject's own secretions. It was presumed that the agents that produced these two types of illness were filterable viruses.

A brief account of the plan of study and the nature of the work in progress at the Harvard Hospital in England has recently been given.<sup>6</sup> This work was directed chiefly at attempts to cultivate and propagate the virus of the common cold in embryonated hen's eggs. It was calculated that there was about a 75 per cent chance of success with this method, because it had already proved successful in about three fourths of the attempts with sixty other viruses. Human volunteers were used to test the infectivity of the test materials. The source of the infective material was a pool of secretions obtained from twenty boys with colds

during an epidemic at Harrow, this had been stored at  $-76^{\circ}\text{C}$  (in carbon dioxide snow).

The first results reported by the British workers indicate that the material retained its infectivity after at least four and a half months' storage at  $-76^{\circ}\text{C}$ , for one month at  $-10^{\circ}\text{C}$  and for three days in an ordinary refrigerator ( $4^{\circ}\text{C}$ ). The upper limit of the size of the infective agent was determined by passing it through graded filters, but the lower limit has not yet been defined. The incubation period of the disease produced was found to be two or three days in most subjects, but occasionally it was five or six days.

An interesting feature of the British studies is the source of the volunteers that were obtained. These were recruited at first among students during their holidays, but others readily became available as news of the work spread. The facilities were arranged to care for only twelve pairs of subjects at a time, different groups being started at intervals of two weeks. The success of the recruiting methods and the satisfaction of the volunteers with the way they were treated are attested by the fact that subjects are now booked for many months in advance. Moreover, many of the volunteers have expressed the desire to serve again and have been allowed to do so, but only after a lapse of six months.

Additional researches on the common cold are being carried out in this country by workers of the National Institute of Health under the direction of Dr Norman Topping.<sup>7</sup> Some of the subjects of these studies are being recruited from inmates of a reformatory. These studies have only recently gotten under way.

All these investigations and others that may be in progress or that are being contemplated hold forth great promise for the solution, in the not too distant future, of many of the problems of the common cold, including its etiology, its epidemiology and perhaps even its treatment and prevention.

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## MASSACHUSETTS MEDICAL SOCIETY

### BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

### DEATHS

**KINLOCH** — Raymond A Kinloch, M.D., of Springfield, died on July 5. He was in his seventy-third year.

Dr Kinloch received his degree from University of Vermont College of Medicine in 1903. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and a daughter survive.

**PREBLE** — Wallace Preble, M.D., of Cambridge, died on February 22. He was in his ninetyeth year.

Dr Preble received his degree from Harvard Medical School in 1883.

A daughter survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RELOCATION OF WASSERMANN LABORATORY

The Wassermann Laboratory of the Massachusetts Department of Public Health has been moved to the Bussey Building, 281 South Street, Jamaica Plain, Boston 30. The telephone number of the laboratory is ARNold 1232.

### NEW APPOINTMENTS

William D Wellock, D.M.D., M.P.H., a Navy veteran and a recent graduate of the Harvard School of Public Health, has been appointed director of the Division of Dental Health. His private practice in Boston was interrupted by the outbreak of the war. As a commander in the United States Naval Dental Reserve, Dr Wellock served in the Alaskan Theater of Operations for more than two years. He received the degree of Master of Public Health from the Harvard School of Public Health following his separation from the Navy. Dr Wellock succeeds Dr A Laurence Corbman, who has heretofore served as acting director of the division.

Grace E Lutman, M.D., M.P.H., Dr P.H., a former assistant district state health officer in the

New York State Department of Health, has been appointed supervisor of Clinics for Crippled Children. Dr Lutman will administer the state clinics located in Salem, Brockton, Springfield, Fall River, Pittsfield, Lowell, Haverhill, Hyannis, Worcester, Greenfield and Gardner.

William W Wood, M.B.A., is serving as survey administrator in the Bureau of Hospital Survey and Construction. A Navy veteran, Mr Wood saw service in the Atlantic, Pacific, Mediterranean and Caribbean theaters.

Francis W Hooper, M.D., has been appointed district health officer of the South Metropolitan District, with headquarters located in Quincy. Prior to his appointment, Dr Hooper saw eighteen months' service in the European Theater of Operations as a captain in the Army Medical Corps. He formerly practiced medicine in Westwood, Massachusetts.

## MISCELLANY

### NOTES

Dr Monroe Davis Eaton became associate professor of bacteriology and immunology at Harvard Medical School on July 1. Dr Eaton was born in Stockton, California, in 1904. He received his collegiate education at Stanford University, where he received an A.B. degree in 1927 and an A.M. degree in 1928. He graduated from Harvard Medical School in 1930, and for three years served as assistant in bacteriology and immunology in that school. Between 1933 and 1936 he was an instructor in bacteriology at Yale University School of Medicine, from 1936 to 1937 he was assistant professor of bacteriology and immunology at Washington University School of Medicine, and in 1937 he became a member of the staff of the International Health Division of the Rockefeller Foundation, as well as director of the Research Laboratory of the California State Department of Public Health.

Dr Donald G Anderson, until recently dean of the Boston University School of Medicine, has assumed the post of secretary of the Council on Medical Education and Hospitals of the American Medical Association.

## CORRESPONDENCE

### DANGERS OF POOLED PLASMA

*To the Editor* During the past year, four patients have died at our hospital because of severe liver disease following the infusion of "pooled plasma" at other institutions, and in all cases, the use of plasma had been ill advised. The indications for employing plasma are quite rare. If it must be used, it should be obtained from the blood of an individual donor who can be carefully checked for an antecedent history of jaundice or infectious hepatitis. That plasma is not a substitute for whole blood became obvious in the treatment of war casualties. That "pooled plasma" caused many deaths three to five months after the completion of brilliant surgery during the war years should militate against its use in civilian practice.

ALFRED HURWITZ, M.D.  
Chief of Surgical Service

Veterans Administration Hospital  
Newington 11, Connecticut

### UNAUTHORIZED USE OF CORRESPONDENCE

*To the Editor* Recently, physicians in Boston, and possibly elsewhere, were circularized by a pharmaceutical house called the Chal-Yon Corporation. This corporation has launched a campaign advertising a product called Chal-Yon which,

among other things, is said to be effective against fungus infections. Included with a description of the therapeutic accomplishments of their product is a statement bearing my signature and dated August 2, 1946, to the effect that this material is nontoxic. The letter from which this statement was taken was addressed to an individual in response to his inquiries whether, in my opinion, the material was nontoxic.

In the statement that appears with the advertisement, my letterhead and signature are carefully reproduced but other parts are conveniently deleted. This abbreviated letter was distributed by the Chal-Yon Corporation, the existence of which I was entirely unaware (if, in fact, it did exist at all at the time) until the letter made its appearance in the mails. The effect of the letter is such that it appears to be a signed statement of indorsement not only by me but also by my associates, whose names appear on the letterhead.

I wish to inform those physicians who have received the circular that the use of this statement was entirely unauthorized. It was written to an individual and was in no way intended as an indorsement of the product recently advertised.

LEWIS W. KANE, M.D.

311 Beacon Street  
Boston 16

## BOOK REVIEWS

*Acetanilid. A critical bibliographic review.* By Martin Gross M.D. With an introduction by Howard W. Haggard M.D. 8°, cloth, 155 pp., with 8 illustrations. New Haven: Connecticut Hillhouse Press, 1946. \$3.00.

The appearance of many sensational articles in the press regarding certain generally used drugs — acetanilid for example — has led to considerable discussion, some of it unscientific, and to controversial utterances by authorities concerning the difficulties and dangers in the use of this drug.

This book takes a step toward fact finding in the field of the intoxications, in which emotional attitudes and neglect of human factors have held sway in the past. Dr. Gross reviews the literature and includes a full length view of what acetanilid is and incidentally what it is not, described in terms of what acetanilid does and does not do. He does not minimize the difficulties in — and the necessity of — determining exactly how toxic acetanilid is — a matter that has been grossly obscured by uncritical alarmists in the past who have attributed to that drug alone the complicated end results of deficiency disease, chronic alcoholic addiction and various psychologic disorders that long antedated the invention of acetanilid. He points out its place in medicine, and outlines broadly its effectiveness as an analgesic.

This book does not contain a host of fresh facts. Rather it reinterprets many of the older and basic articles on acetanilid in the more recent light of psychologic and psychosomatic medicine. The best chapter deals with the question of addiction to acetanilid, a minor problem according to this author's figures. This chapter summarizes the whole problem of addiction and habituation in general as well as the particular aspects that apply to acetanilid.

*Medical Education and the Changing Order.* By Raymond B. Allen, M.D. Ph.D. Studies of the New York Academy of Medicine, Committee on Medicine and the Changing Order. 8°, cloth, 142 pp. New York: The Commonwealth Fund, 1946. \$1.50.

Dr. Allen is executive dean of the College of Dentistry, Medicine and Pharmacy of the University of Illinois. His monograph was prepared under the auspices of the Committee on Medicine and the Changing Order established by the New York Academy of Medicine and is one of a series, each one of which is interesting.

The author presents a readable account of medical education describing first its historical background and later following the trends that have appeared to modify its course. His comments are shrewd and searching. He agrees with most medical educators that it appears difficult to attract to the study of medicine as high a type of student as is desirable because, in part, of the high cost in time and money. He gives many hints about medical education and how to make it more useful. He suggests, for example, that the curriculum

is not entirely perfect that pedagogic methods employed are not wholly adequate and that many internships — admittedly a vital part of a doctor's education — are not all they might be.

Dr. Allen concludes with a forecast: the cost of medical education will not diminish — there is no more crucial problem facing medical care than the distribution of doctors and that although in the past the services of medicine, like those of religion, have been largely personal and although there will always be a need for personal services, medicine of the future if it is to progress as a social as well as a biologic science, must broaden its outlook and adjust its educational program accordingly.

*The Centennial of Surgical Anesthesia. An annotated catalogue of books and pamphlets bearing on the early history of surgical anesthesia.* Compiled by John F. Fulton, M.D. and Madeline E. Stanton A.B. 8°, paper 102 pp. with 8 facsimiles and one portrait. New York: Henry Schuman, 1946. \$4.00.

The compilers of this catalogue have assembled an excellent collection of literary material on the subject of surgical anesthesia. The period covered is from the time of Pliny and Dioscorides (A.D. 50 to 100) to the discovery of the use of ether in the United States in 1842–1846 and of chloroform in England in 1847 and to the rediscovery of nitrous oxide in 1863. The catalogue is divided into eight major divisions with a short historical introduction to each division, and the major items are annotated. The catalogue is limited to items exhibited at the Yale Medical Library in October 1946 either in the original or in facsimile. Naturally emphasis is placed on experimental work in the United States.

The first section concerns the forerunners of surgical anesthesia and includes the Greek and Roman authors and their references to mandragora and the soporific sponge, the use of physical agents, such as the snow and ice-cold water of Avicenna and Severinus and the method of nerve compression of James Moore (1784) nitrous oxide, carbon dioxide and the anesthetic agents, mesmerism and hypnotism and the early writings of Cordus (1561) and Turner (1743) on sulfuric ether. Subsequent sections are devoted to the American claimants of the discovery of surgical anesthesia: Crawford W. Long, Horace Wells, William T. G. Morton and Charles T. Jackson. Each lists in detail the original papers of the author, and title pages are reproduced in facsimile. The story of the controversy is presented in a factual manner without an endeavor to pass judgment on the merits of the matter. To each of these divisions is appended a list of references on biography and commentaries.

A large section which is concerned with the writings of and about Morton includes a census of the known copies of the Morton publications. (Since the publication of this catalogue the Boston Medical Library has acquired a copy of the rare third edition of Morton's fourteen-page *Lithicon* the earliest of this series to be located in any collection, public or private.)

Another section describes the discovery of chloroform and its use by Sir James Y. Simpson. During 1847 and 1848 the medical literature of the world became flooded with articles about ether anesthesia and in 1848 about chloroform. The seventh section comprises a list of references to publications of this period on ether, chloroform and other agents including opiates and nitrous oxide and mesmerism followed by a short list of early general monographs on surgical anesthesia and a note on anesthesia and psychiatry in which is described *The Anesthetic Revolution and the Gift of Philosophy* (1847) by Benjamin P. Blood. The concluding section comprises a long list of journal articles, monographs and addresses on the history of the subject.

The catalogue is printed and published in a de luxe manner and should be in all medical history collections.

*The Diagnosis and Treatment of Bronchial Asthma.* By Leslie W. Gay, Ph.D. M.D. With a foreword by Warfield R. Longcope, M.D. 8°, cloth, 334 pp., with 80 illustrations. 5 plates and 39 tables. Baltimore: Williams and Wilkins Company, 1946. \$5.00.

In recent years a number of encyclopedic books have been published on allergic diseases. Brief summaries are contained in systems of medicine. Dr. Gay has written a book

- 5 Abernethy, T J Experimental transmission of minor respiratory illness to human volunteers (Soc Proc) *J Clin Investigation* 25 911, 1946
- 6 Reports of Societies Common cold research unit interim report on transmission experiment *Brit M J* 1 650-652, 1947 Also Editorial Research on common cold *Ibid* 1 645, 1947
- 7 Washington Letter National Institute of Health continues research on common cold *J A M A* 132 84, 1946 New facilities aid research on common cold *Ibid* 132 929, 1946 Reformatory inmates to assist in research on common cold *Ibid* 132 1016, 1946

## MASSACHUSETTS MEDICAL SOCIETY

### BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

### DEATHS

**KINLOCH** — Raymond A Kinloch, M D, of Springfield, died on July 5. He was in his seventy-third year.

Dr Kinloch received his degree from University of Vermont College of Medicine in 1903. He was a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

His widow and a daughter survive.

**PREBLE** — Wallace Preble, M D, of Cambridge, died on February 22. He was in his ninetieth year.

Dr Preble received his degree from Harvard Medical School in 1883.

A daughter survives.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### RELOCATION OF WASSERMANN LABORATORY

The Wassermann Laboratory of the Massachusetts Department of Public Health has been moved to the Bussey Building, 281 South Street, Jamaica Plain, Boston 30. The telephone number of the laboratory is ARNold 1232.

### NEW APPOINTMENTS

William D Wellock, D M D, M P H, a Navy veteran and a recent graduate of the Harvard School of Public Health, has been appointed director of the Division of Dental Health. His private practice in Boston was interrupted by the outbreak of the war. As a commander in the United States Naval Dental Reserve, Dr Wellock served in the Alaskan Theater of Operations for more than two years. He received the degree of Master of Public Health from the Harvard School of Public Health following his separation from the Navy. Dr Wellock succeeds Dr A Laurence Corbman, who has heretofore served as acting director of the division.

Grace E Lutman, M D, M P H, Dr P H, a former assistant district state health officer in the

New York State Department of Health, has been appointed supervisor of Clinics for Crippled Children. Dr Lutman will administer the state clinics located in Salem, Brockton, Springfield, Fall River, Pittsfield, Lowell, Haverhill, Hyannis, Worcester, Greenfield and Gardner.

William W Wood, M B A, is serving as survey administrator in the Bureau of Hospital Survey and Construction. A Navy veteran, Mr Wood saw service in the Atlantic, Pacific, Mediterranean and Caribbean theaters.

Francis W Hooper, M D, has been appointed district health officer of the South Metropolitan District, with headquarters located in Quincy. Prior to his appointment, Dr Hooper saw eighteen months' service in the European Theater of Operations as a captain in the Army Medical Corps. He formerly practiced medicine in Westwood, Massachusetts.

## MISCELLANY

### NOTES

Dr Monroe Davis Eaton became associate professor of bacteriology and immunology at Harvard Medical School on July 1. Dr Eaton was born in Stockton, California, in 1904. He received his collegiate education at Stanford University, where he received an A B degree in 1927 and an A M degree in 1928. He graduated from Harvard Medical School in 1930, and for three years served as assistant in bacteriology and immunology in that school. Between 1933 and 1936 he was an instructor in bacteriology at Yale University School of Medicine, from 1936 to 1937 he was assistant professor of bacteriology and immunology at Washington University School of Medicine, and in 1937 he became a member of the staff of the International Health Division of the Rockefeller Foundation, as well as director of the Research Laboratory of the California State Department of Public Health.

Dr Donald G Anderson, until recently dean of the Boston University School of Medicine, has assumed the post of secretary of the Council on Medical Education and Hospitals of the American Medical Association.

## CORRESPONDENCE

### DANGERS OF POOLED PLASMA

*To the Editor* During the past year, four patients have died at our hospital because of severe liver disease following the infusion of "pooled plasma" at other institutions, and in all cases, the use of plasma had been ill advised. The indications for employing plasma are quite rare. If it must be used, it should be obtained from the blood of an individual donor who can be carefully checked for an antecedent history of jaundice or infectious hepatitis. That plasma is not a substitute for whole blood became obvious in the treatment of war casualties. That "pooled plasma" caused many deaths three to five months after the completion of brilliant surgery during the war years should militate against its use in civilian practice.

ALFRED HURWITZ, M D  
Chief of Surgical Service

Veterans Administration Hospital  
Newington 11, Connecticut

### UNAUTHORIZED USE OF CORRESPONDENCE

*To the Editor* Recently, physicians in Boston, and possibly elsewhere, were circularized by a pharmaceutical house called the Chal-Yon Corporation. This corporation has launched a campaign advertising a product called Chal-Yon which

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## SOME OBSERVATIONS ON TRANSURETHRAL PROSTATIC RESECTION\*

REED M. NESBIT, M.D.†

ANN ARBOR, MICHIGAN

WHEN resident surgeons are taught the performance of transurethral prostatic resection at the University of Michigan Hospital and when matters pertaining to resection are discussed with visiting urologists, it has appeared desirable to emphasize certain details of technic that have been found necessary to the successful execution of operation. Many of these appear not to have been adequately elaborated on in the literature, and for that reason it seems appropriate to report some of the particulars that are considered to be fundamental.

The earliest description of operative procedures, purposefully designed to relieve obstructive uropathy, was written by Ambroise Paré, who, in the sixteenth century, recognized the existence of lesions that he termed "carcinosis" and removed with instruments of his own design. Paré's instruments were introduced through the urethra and effected the removal of the obstructing tissue by a scraping or "shearing" maneuver. It is probable that the lesions described by Paré were urethral strictures, for they appear to have been located in the urethra and their presence was antedated by a purulent discharge.

Prostatism was first recognized at the beginning of the nineteenth century, and all the earliest approaches to the relief of the disease were made via the urethral route. The surgeons of that day were adept at the division of strictures and were experts at crushing vesical calculi, and it was therefore natural that they should improvise on their familiar technics in the treatment of the newly discovered disease, rather than develop new and revolutionary procedures.

The ingenuity that was exercised by our urologic predecessors of this period was most interesting and attested to their great skill, as well as to the urgency of the problem that confronted them. The direct surgical attack on the prostate gland was delayed until the Listerian era, when surgical versatility became possible.

All the early intraurethral operations failed of their purpose, since none of them cured prostatism because they did not effect the removal of obstructing tissue. This was first successfully accomplished when methods of enucleation were discovered, and until the modern resectoscope was invented, surgeons were required to perform open operations to extirpate the abnormal prostate. Now the diseased gland can be removed safely through the urethra, and many of the well recognized hazards, as well as inconveniences, of open prostatectomy may thus be eliminated.

The resectoscope of today is a product of modern inventive genius. It owes its existence to three fundamental discoveries: the incandescent light, the high-frequency current and the fenestrated sheath. With this device the surgeon is able to excise tissue rapidly and with a minimum of tissue destruction; he is able, at all times, to orient himself perfectly within the field of operation and, with the help of the magnifying-lens system employed in modern instruments, to identify more accurately than with the unaided eye all structures within the field of operation. Bleeding is under complete control, and by employing instruments that can be operated completely with one hand, the surgeon is able to use his free hand for rectal palpation, which provides him with tactile, as well as visual, guidance during operation.

Most urologists have employed this method in treating urinary obstructions. Some have found only a limited scope of usefulness for the procedure, whereas others have perfected technics that have enabled them successfully to employ resection exclusively in the treatment of all obstructions at the bladder neck. Our position at the University of Michigan Hospital has been somewhere between the two extremes. We have made continuous efforts to explore objectively the ultimate possibilities of the method, but meanwhile have endeavored to maintain a balance of technical advance in the other types of prostatectomy consonant with our responsibilities in the training of well rounded resident surgeons.

\*Presented at a meeting of the New England Section of the American Urological Association, Boston, November 14, 1946.

†From the Department of Surgery, University of Michigan Medical School.

†Professor of urology, University of Michigan Medical School.

The first patient on whom transurethral prostatic resection was performed in the University of Michigan Hospital in October, 1931, enjoyed a comfortable and uncomplicated convalescence and left the hospital a few days after operation proclaiming widely the miracle that he considered had been performed on him. His basis for opinion in the matter was extremely limited, consisting only of a comparison of his hospital experience with that of all the other patients on the ward, who were convalescing from suprapubic and perineal prostatectomies. But our own experience in the matter was equally limited, so that our immediate enthusiasm was perhaps not entirely unjustified. A less spectacular result in the first case would doubtless have resulted in a more conservative appreciation of the operation's potentialities, for during the years that followed it was constantly hoped that each successive patient would enjoy the beneficent results that the first patient had derived. The naïveté of this attitude probably explains why subsequent failures and disasters did not arouse a feeling of condemnation for the operation, but rather stimulated critical evaluation of its performance. Experience has shown that prostatic resection possesses many attendant hazards and that there are numerous pitfalls in the performance of this technically difficult operation. Most of these can be considered under the headings of trauma and hemorrhage.

### *Trauma*

One of the most frequent causes of both immediate and late complications after resection is urethral trauma, for the standard resectoscope has a large, rigid sheath, and all urethras do not readily accommodate it. When the urethra is traumatized by forceful introduction of instruments that are too large, or insulted by a snugly fitting sheath in the urethra during a long operation, certain grave sequelae are inevitable. The introduction of infection, which is likely to occur as an immediate complication, is manifested by the development of local tenderness of the urethra and general sepsis, later, the development of stricture completes the cycle and may leave the patient with a lesion that is just as debilitating and infinitely more difficult to treat than prostatism. Urethral trauma is usually avoided if the surgeon is careful not to introduce the standard-size resectoscope into a urethra that fails to accommodate easily a No. 30 Fr steel sound. When smaller urethras are encountered, alternative technics can be employed. One consists of the use of a resectoscope having a sheath of smaller than standard diameter.

At present a McCarthy instrument with a sheath diameter of No. 24 Fr is available, and it is hoped that in the near future instruments will be constructed so that one working element can be employed with various loops and sheaths in sizes No. 24, 26 and 29 Fr. If the use of smaller instru-

ments is impractical or impossible, the surgeon has two procedures that can be followed. Meatotomy will often permit the unimpeded passage of the resectoscope, but in some cases the remainder of the urethra is too small after the meatus has been enlarged. Perineal urethrotomy is then indicated. About 35 per cent of the patients operated on by resection in the University of Michigan Hospital require meatotomy, whereas perineal urethrotomy is performed in 20 per cent.

Other indications for perineal urethrotomy include severe urethritis, shortness of the penile suspensory ligament, excessive length of the prostatic urethra and abnormal position of the prostate gland. When a short suspensory ligament is present the curvature of the anterior urethra is exaggerated and causes resistance to the passage of straight instruments. The urethra may be traumatized at the penoscrotal angle, where maximum tension occurs, or the end of the sheath may be thrust downward into the prostatic bed during operation in such a way as to create damage. On one occasion I experienced this disaster while operating on an obese and emphysematous subject. The prostate gland was not large, and the operation was brief. The suspensory ligament was short and caused the resectoscope to be held rigidly in the urethra. Perineal urethrotomy seemed indicated, but was not performed, for it was decided that the small resection could be finished in a few minutes. When the operation had been completed and a catheter introduced, there was an abnormal amount of bleeding, so that the instrument was reintroduced for the purpose of arresting it. While this was being done, the patient coughed violently, and the force thus created caused the resectoscopic sheath to penetrate through the floor of the prostatic capsule. He later died of pelvic cellulitis. This tragedy would not have occurred if the resectoscope had been contained lightly in the urethra, for the force exerted by the cough would easily have moved the instrument rather than causing the patient to be impaled on it.

In some cases in which the prostatic urethra is long or the prostate gland is situated high in the pelvis, the resectionist is required to exert pressure on the instrument to insert it far enough to be in a proper position for operation. The employment of even this small amount of force in the handling of the resectoscope can be avoided if perineal urethrotomy is utilized. In performing resection on large glands—that is, those in which 50 gm or more of tissue is removed—we have employed urethrotomy in 30 per cent of cases, in comparison to 20 per cent for all cases. In the resection of large glands the procedure has allowed an increased maneuverability that has facilitated the technic of operation.

It can be accepted as an axiom of transurethral prostatic surgery that the resectoscope must be freely and easily contained by the urethra at all

times The instrument that is held tightly in the urethra under any circumstances cannot be maneuvered successfully or safely by the surgeon in the performance of an operation that requires delicate and precise dissection The single exception to this rule is when the instrument is held tightly in the prostatic urethra by cancer or by a vesical-neck contracture Whenever perineal urethrotomy is indicated to effect this purpose, it should be done, for it is simple to perform and patients suffer little or no inconvenience from it. They rarely pass urine through the incision, and none develop stricture at the site of operation

Another form of traumatic injury occurs when the resectionist cuts too deeply into vulnerable areas The most frequent are perforation of the prostatic capsule and injury of the external urinary sphincter Minor perforations of the prostatic capsule often occur in the performance of transurethral resection by surgeons who attempt a subtotal removal of the gland These minor perforations rarely give rise to morbidity and are probably of little clinical significance—a circumstance that on certain occasions has permitted me deliberately to excise a small portion of the capsule with the resectoscope, either for the purpose of biopsy or to demonstrate to a visiting urologist that the structure in question was actually the prostatic capsule When small perforations occur the healing of the defect probably takes place quite rapidly and is enhanced by the catheter diversion of the urine. Extensive perforation may give rise to pelvic cellulitis and extravasation, and if not recognized and promptly treated by adequate drainage, will terminate fatally The average resectionist, however, is adequately oriented at all times and is able to recognize any perforations of the capsule that occur If the perforation is extensive, he can perform immediate suprapubic drainage, if it is small or of dubious size, he can remain on the alert for the development of unfavorable symptoms

Urinary incontinence following transurethral resection is much like the weather—a great deal has been said, but little done about it. It occurs when the external sphincter is cut with the resectoscope—an accident of technic that can easily be avoided in the hands of the average resectionist This complication has occurred in only 3 cases in the University of Michigan Hospital series, and in view of the fact that nearly half the operations were performed by various members of the resident staff, it is at once evident that it can be avoided by even the inexperienced resectionist if due care is exercised in the performance of a sound technic Except in the presence of infiltrating cancer or inflammatory contracture that involves the membranous urethra, the proximal margin of the external sphincter can be recognized with the foreoblique-lens system, which affords perfect illumination and great magnification of the tissues in the field of vision Recognition of the upper sphincter margin is made

possible by certain anatomic properties of the structures that go to make up the area These structures have been described as follows

The fixed portion of the urethra includes the prostatic and the membranous portions the membranous urethra is the only part that has practically no mobility The prostatic portion may be moved slightly within the limits allowed by the pubo-prostatic ligaments and by the connection of its capsule with the superior layer of the triangular ligament in front and the recto-vesical fascia and rectum beneath and above.<sup>4</sup>

Thus, anatomically, the membranous urethra is an immobile structure, whereas the adjoining prostatic urethra is slightly movable, but the mucosa of each structure is tightly adherent. When the prostate gland is moved, the surface configuration at the prostatomembranous junction is altered by wrinkling in a manner comparable to the wrinkling of the bellows that connects two Pullman cars The mucosal folds that are created in this manner are transversely disposed and extend around the entire circumference of the urethra They can be recognized easily when observed through the resectoscope, and are brought into view most effectively if the instrument is moved in and out through a short excursion while the area is being inspected Fortunately, this wrinkling phenomenon tends to increase as transurethral resection progresses because of the increased mobility of the gland that is effected by the operation, so that the surgeon can always demonstrate the prostatomembranous junction toward the end of the operation and can safely excise tissue down to that point without fear of sphincter injury

### Hemorrhage

Every prostatic resection is accompanied by blood loss Often, the amount is negligible, but it may be considerable and can materially influence the morbidity and mortality It is important, therefore, that the resectionist have more or less accurate information regarding the amount of blood loss, rather than relying on impressions gained during the performance of operation, for significant losses can occur and escape notice while he is concentrating his attention on the details of operative technic.

A simple method that can be employed for the estimation of blood losses after resection was described by Nesbit and Conger<sup>1</sup> in 1941 This procedure takes only two or three minutes and provides the surgeon immediately with objective data regarding the patient's need for replacement therapy When resection is undertaken in feeble and debilitated patients or those with extremely large prostates it is often advisable to start the administration of blood at the beginning of operation

The successful control of bleeding during operation depends a good deal on certain details of technic that are generally acquired with experience Bleeders are quite easily recognized and can be quickly arrested when the walls of the prostatic fossa are



smooth and clean, for then the resectionist is able rapidly to survey the entire operative field from a vantage point at the membranous urethra. But when the operative field has an irregular and uneven surface, bleeding points are not readily seen from such a panoramic survey, finding them often requires a long and painstaking search, and the roughness of the irregular surface tends to increase the difficulties in question by enhancing the formation of blood clots, which in turn conceal under-

each excursion of the cutting loop extend the full length of the adenomatous mass that is being resected. When long masses of tissue are to be excised the operator, while cutting, may slide the sheath of the instrument toward himself with the loop extended, so that longer slices of tissue than would otherwise be permitted by the full excursion of the loop can be excised. One can frequently remove pieces of tissue that are 5 cm. or more in length by sliding the resectoscope during the cut-



FIGURE 1 Plaster Moulage Indicating the Manner in Which a Lateral Lobe of the Prostate Is Dissected Out

*In this case, with the left lateral lobe (P) involved, the resection is started near the top of the lobe and is deepened laterally and downward to dissect the lobe away from the prostatic capsule (C)*

lying bleeders. Our resident surgeons who are beginning to learn the operation often have considerable difficulty in finding bleeders. When their more experienced preceptors take over, they usually encounter a field of operation resembling plowed ground, in which bleeding points are most difficult to identify. To clarify the situation, it is necessary to eliminate the peaks and furrows by long, continuous sweeps with the cutting loop. After the walls of the fossa have been leveled off, little difficulty is encountered in finding and stopping bleeders. The experienced resectionist strives to make

the process. In employing this technic, however, the surgeon should always remember that the tissue that is being traversed must be kept under direct vision at all times, and that every landmark must be visible while the instrument is in motion. When the distal end of the adenomatous mass comes into view, the movement of the sheath is stopped, and the cutting loop is pulled forward and finally appears within the sheath shearing off the fragment. The instrument is then kept in place while the tissue fragment floats away in the stream of water flowing through the sheath, permitting an unimpeded view

of the excavation, and the operator can either arrest bleeding within the excavation or continue to carry out his cutting maneuvers. By a technic of this sort, the cut surface can be kept smooth and free from bleeding points and blood clots during operation.

The injection of various vasoconstrictive substances into the prostate gland to lessen the amount of bleeding during operation has been advocated by some authors. When these substances are injected, the bleeding is often reduced to a remarkable extent. In fact, some of the glands do not bleed at all during resection. But when the vasoconstriction dis-

operative irrigations of the bladder. After the O'Connor technic had been employed with great success — and incidentally with the elimination of a vast number of hours of nursing — a question was raised regarding the reason for success of the method, since the O'Connor technic had brought about two distinct changes in the routine of postoperative care: the employment of thrombin and the elimination of irrigations.

To determine which factor was responsible for the success of the method, two series of cases were observed. In one, thrombin was used, and in the other it was omitted, but in both series no irrigations were

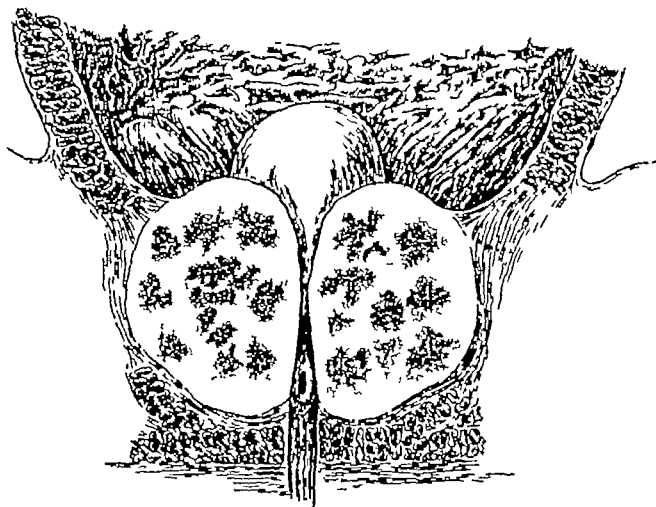


FIGURE 2. Diagram Showing Obstruction at the Bladder Outlet Produced by Hypertrophy of the Two Lateral Lobes and the Median Lobe of the Prostate

appears, a subsequent vasodilation occurs and some of the patients bleed excessively. None of the methods of injection that have been proposed thus far are to be recommended.

The postoperative control of bleeding is another problem that concerns the resectionist. Formerly, it was our practice routinely to irrigate the bladder with water every ten or fifteen minutes during the first twenty-four hours after operation. This was done in an effort to prevent excessive bleeding and to ensure against blockage of the catheter with blood clots. Some resectionists employ continuous irrigation for the same purpose. About two years ago, Dr Vincent O'Connor<sup>2</sup> described a method of controlling postoperative bleeding by instilling thrombin into the prostatic fossa via the catheter following resection. For the thrombin to effect hemostasis it was necessary to eliminate all post-

carried out. Determinations of postoperative blood loss were made in all cases, and the amounts were the same in both series. The results of these studies have been reported in a publication by Ratliff and Plumb.<sup>4</sup> We now employ no thrombin and do not irrigate after resection. There have been fewer cases of catheter blockage than ever before, and the nursing department is delighted to have been relieved of the incessant and onerous duty that was previously its lot.

#### Operative Technic

A short resume of a technic that has been successfully employed in prostatic resection is presented. In this procedure there are three phases of operation: in the first a cone of tissue is removed — the apex of the cone is at the apex of the prostate, and the base of the cone is encircled by the internal

vesical sphincter, the second phase consists of removal of the remaining lateral-lobe structures from within the concave prostatic fossa, and the third phase is concerned with a careful removal of the apex masses of tissue abutting on the external sphincter. In the first phase of operation the resectoscope is

end of the lobe just lateral to the commissure and is drawn forward along with the resectoscope, and a fragment of tissue extending the full length of the lateral lobe mass is excised and allowed to float into the bladder. The surgeon immediately inspects the furrow that remains, coagulates any bleeding points

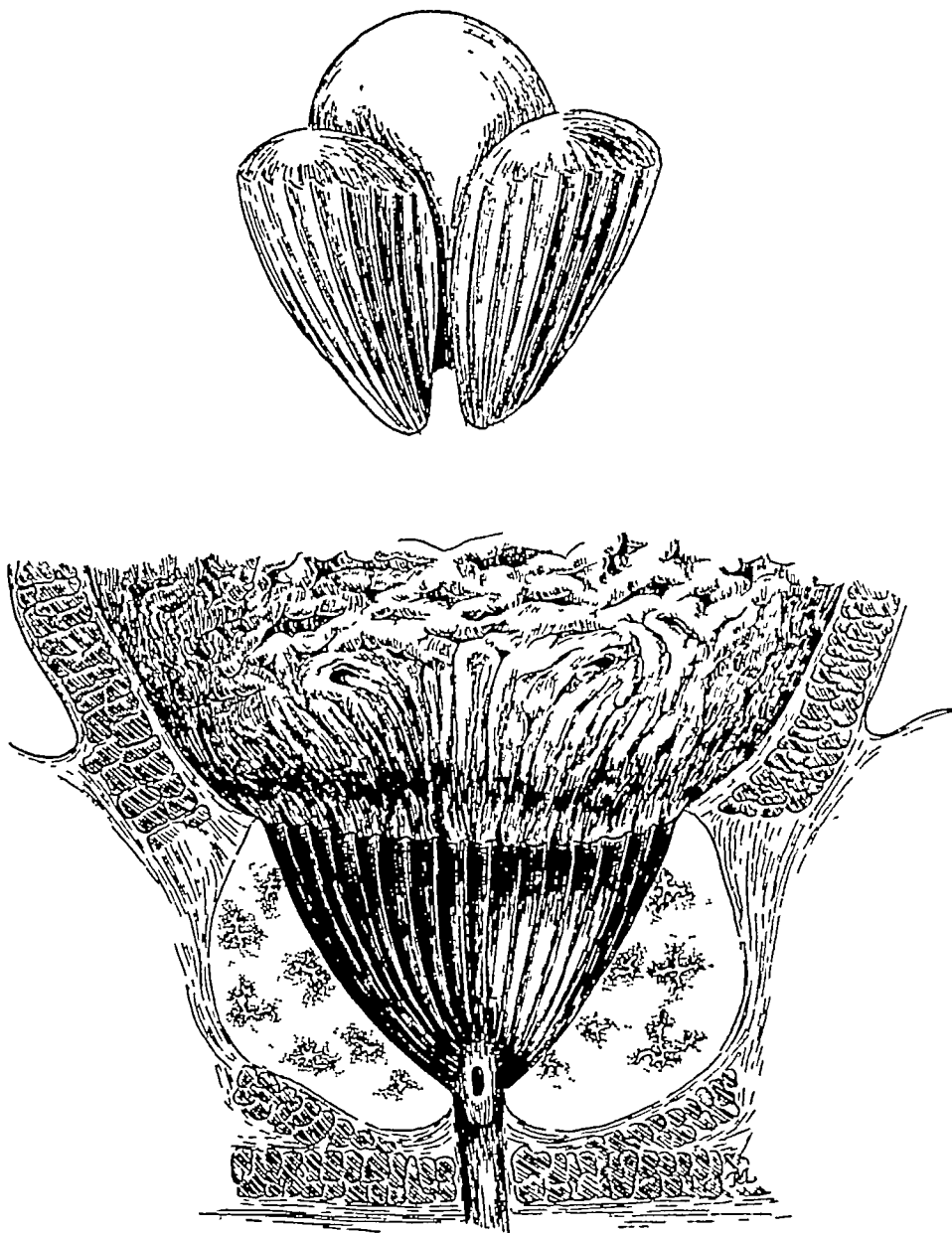


FIGURE 3 Diagram Showing the Cone-Shaped Area Left after the First Phase of the Operation Has Been Completed

Although a large part of the median and lateral lobes has been removed, there still remains much prostatic tissue to be removed from the concave prostatic fossa

rotated so as to enable inspection of the anterior wall of the prostatic urethra. The anterior commissure is observed, and one of the lateral-lobe masses is often found to bulge more prominently than the other into the field of vision. This one is chosen for the beginning of the operation. The extended cutting loop is brought into contact with the cephalad

and carefully inspects the morphology of the tissues that have been laid bare.

The observation of tissue morphology during operation is of primary importance, for it is only in this manner that the surgeon is guided in determining what should not be excised. The tissues of the adenomatous mass have a characteristic appear-

ance that varies only when there is an excessive leiomyomatous stroma. The appearance of the compression capsule is different from that of either the normal or the adenomatous prostate gland, it has a sort of asbestos appearance when viewed through the foreoblique-lens system. Infiltrating cancer is identified by its cellularity. The internal sphincter is easily recognized by its circular muscle fibers, and the prostatic capsule has a fibrous appearance that facilitates identification.

During resection, if only prostatic tissue is identified in the initial furrow, another fragment of

apex of the prostate converge at a point, for the membranous urethra is a fixed point. Thus, the confluent furrows that successively expose the circumference of the internal sphincter create a cleft extending from that circle out to the apex, and the cleft that is created in the manner described often encircles sizable masses of prostate (Fig 1). These masses are composed of portions of the lateral lobes and of the median lobe, and when encircled as described and cut off from peripheral circulation, the entire mass can be cut up into fragments quickly and bloodlessly. In the resection of small obstructing

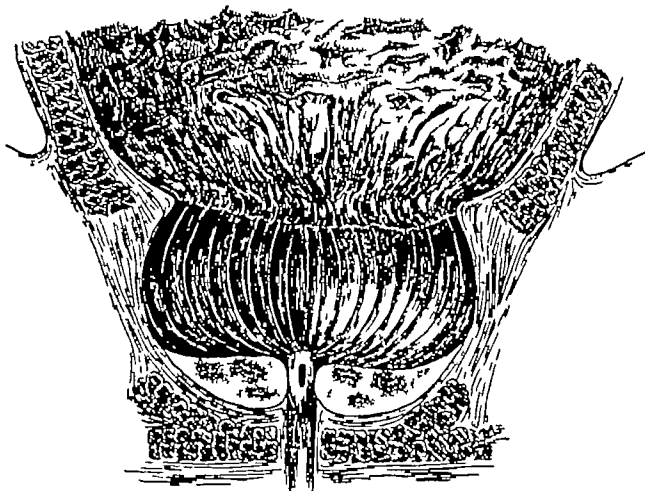


FIGURE 4 Diagram Showing How the Prostatic Tissue Is Removed from the Concave Fossa down to the Capsule of Prostate

*At the conclusion of this second phase of the operation, there remains only some prostatic tissue at the apex of the gland adjacent to and just above the external voluntary sphincter muscle. In the third stage of the operation this remaining tissue at the apex of the prostate gland is removed.*

tissue can safely be excised in the same line, but if muscular fibers are recognized at the inner end of the furrow, the operator must cut no deeper at that point. Instead, the resectoscope is rotated a few degrees laterally so as to begin its next excision of a tissue fragment. This slice of tissue and each successive one extend, like the first fragment, the full length of the prostate gland, and the furrow that is formed by the second cutting stroke is confluent with the first, and, like the first furrow, is deepened until the circular fibers of the internal sphincter are encountered, then the resectoscope is again rotated a few degrees, and another adjoining furrow is made. It is noteworthy that each of the successive cuts exposes a small arc of the internal sphincter but that the individual furrows extending toward the

glands or contractures, the cutting maneuvers in the first zone of operation often entail only the removal of a shallow depth of tissue, so that there may be no encirclement of a tissue mass. When the first phase of operation has been concluded, there is a cone-shaped space extending from the apex of the gland to the circle described by the internal vesical sphincter. The walls of this cone are smooth and are composed of prostatic tissue, and any bleeding points are easy to identify (Fig 2 and 3).

The second phase of the operation is concerned with the removal of adenomatous tissue from the concave prostatic fossa. In this zone the cutting loop enters the prostatic mass distal to the circular fibers of the internal sphincter, and each excursion

of the loop extends almost to the external sphincter, where a small mass of tissue is allowed to remain as a bulwark against injury of the sphincter. In this subvesical zone the first cut is made anteriorly, and successive cuts are made in the same furrow until the capsular structures are recognized. Successive cuts are made lateral to the original furrow until capsular structures come into view, and dissection is continued with the object of creating a cleft that is peripheral to the adenomatous mass of tissue. Digital palpation of the prostate gland during the resection within the posterior half of the fossa is essential to accurate and safe dissection, for with a finger in the rectum the surgeon is able to palpate quite accurately the thickness of the adenoma and, when nodular masses are relatively inaccessible because of unusual position, to push them upward into the path of the cutting loop. This maneuver is particularly valuable in the excision of tissue masses situated just beneath the internal sphincter, either in the midline or laterally, where significant masses are often encountered. I have often found it necessary to excise masses of tissue at least 2 cm in diameter that were situated beneath the apex of the trigone. In such cases resection of the adenoma down to the thinned-out capsule could be performed with safety only by accurate palpation, and often these masses of tissue are excised most effectively when they have been pushed upward forcibly by the finger in the rectum. By peripheral dissections in the second zone of operation, the adenomatous mass is devascularized so that the free mass that is finally isolated on the floor of the urethra can be expeditiously and safely excised by rapid resection.

At the conclusion of the second phase of operation, the surgeon is able to survey the entire fossa from a vantage point at the apex of the gland. In the distance he can see the denuded internal sphincter, and in the foreground he is able, by rotating the instrument, to inspect the smooth, concave walls of the prostatic fossa. Bleeding points are readily discovered (Fig 4).

The final phase of operation requires a meticulous and careful dissection, for it is now that the surgeon resects all tissues down to the margin of the external sphincter. This margin is readily identified, as described above, by observation of the transverse fold or wrinkle that is made visible when the resectoscope is moved out and in and rotated while the area in question is inspected. When the outer margin of safe resection has thus been delineated throughout its entire circumference, the excision of apical tissue can be carried out as far as this line. A convenient place to start resection of tissue in this zone is anteriorly, the instrument is then rotated as successive adjoining fragments of the gland are excised until the ejaculatory ducts and the verumontanum are reached, but these structures are not removed. The surgeon must bear in mind that, although the

apex of the adenomatous gland is tapered in form and ends at the triangular ligament, it often extends laterally for some distance on this abutment, and resection at the apex must extend not only down to the urethral level but also deeper on each side of the midline so as to include the removal of all adenomatous tissue contained within the capsule. This is greatly facilitated by rectal palpation during operation. Failure to extirpate the entire apex mass often results in post-resection difficulties, for the remaining tissues expand and project into the urethra and may produce irritation or obstruction.

By employing a systematic approach in the technic of transurethral resection the urologist is enabled to perform a subtotal removal of the prostate gland, and the size of the gland that is removed depends in a large measure on the factors of dexterity and experience in the performance of this operation. Most experienced surgeons today believe that subtotal prostatectomy is essential to the attainment of consistent good results, and when this objective cannot be attained the urologist will be well advised to treat his patient by some enucleative procedure, for the cure of prostatism today, as in Freyer's day, depends on the extirpation of the gland.

\* \* \*

The present report is not concerned with any evaluation of transurethral prostatic resection. To do so would inevitably introduce matters relating to opinion, and debate has never settled the fate of any therapeutic method. Time will eventually determine the ultimate place of transurethral resection in the surgery of the prostate gland.

In conclusion, the following paragraph from a treatise by Deaver<sup>5</sup> is regarded as pertinent.

Whether or not every shred of prostatic substance is removed by Freyer's operation is of very little consequence, who first performed such an operation is of less and whether it is anatomically possible or not is of no consequence at all, since the results in Mr. Freyer's case speak for themselves, and he has aroused the profession not only in his own country but in France and America as well, to the realization of what a brilliant chapter of prostatic surgery is unrolled in his achievements. Indeed were I inclined to criticize the reports of Mr. Freyer's case in any way, it would be to say that they were almost too good to be believed, except when coming from such a source, so much like a fairy story do they read.

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## THE EXAMINATION OF SEROUS FLUIDS BY THE CELL-BLOCK TECHNIC\*

C B CHAPMAN, M D,† AND E J WHALEN, M D †

BOSTON

THAT serous fluids from patients suspected of having malignant tumors may yield information of considerable diagnostic value has been established for many years, and in 1917 Mandelbaum<sup>1</sup> devised a technic for the preparation of cell

has been a steady increase in the number of specimens of serous fluids submitted for examination, and for the past five years, between 150 and 200 specimens have been examined each year. We were led to review the material not only because of the num-

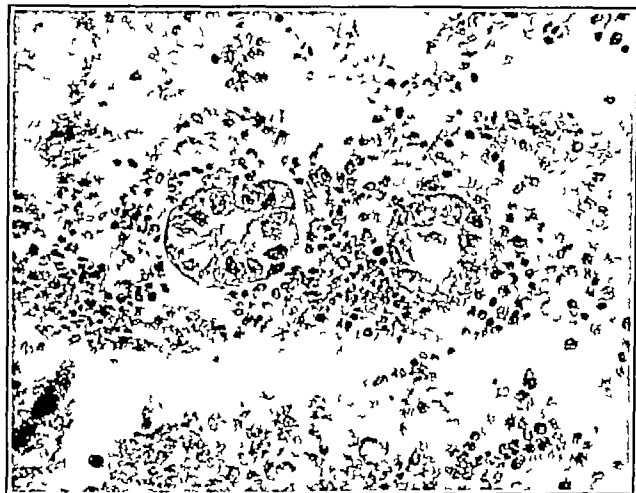


FIGURE 1 *Acini in Sediment from Pleural Effusion Produced by Seeding of Adenocarcinoma of Breast to Pleura (x520)*

*There is moderate anaplasia of the cells composing the acini*

blocks that, with but few modifications, is generally employed at present.

Evaluations of the procedure as employed in various laboratories have been published by a number of workers, including Zemansky,<sup>2</sup> Schlesinger<sup>3</sup> and Honigman,<sup>4</sup> all of whom showed conclusively that, when properly carried out, the method is not only technically practical but also diagnostically useful. Zemansky has traced in some detail the development of the method, and reference should be made to his paper for information of this type.

We cannot ascertain when the first cell block was prepared and examined at the Mallory Institute, but the records show that before 1931 the technic was employed infrequently. Since that time there

has been a steady increase in the number of examinations available but also because clinicians and pathologists alike often express discouragement at the apparently small number of positive results obtained by the use of the technic.

## METHOD

The method that has been in use at the Mallory Institute during the fifteen and a half years covered by this survey is similar to that devised by Mandelbaum, with a few modifications. At present we employ the following procedure:

The fluid sent for examination is allowed to settle overnight in the refrigerator. The supernatant fluid is then decanted, and the cloudy or clotted residual is centrifuged in a tapered 50-cc. tube for thirty minutes at 3000 r p m.

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After centrifuging, the supernatant fluid in the tube is poured off, and Zenker's fluid added. The block is fixed in the tube for twelve hours.

The fixed block is dislodged from the tube by gentle pressure at one edge with a wire loop or the blade of a forceps.

The entire block is placed on its side on filter paper and is sectioned in the usual manner. Stain-

as usual, and 50 or 100 cc is then taken from the bottom of the container. To this portion 10 cc of Zenker's fluid is added to precipitate the protein and to fix the cells in the fluid. This is then centrifuged and prepared in the usual manner.

For a positive diagnosis on a cell-block preparation the following characteristics are required: the presence of fully or partly formed acini or of solid

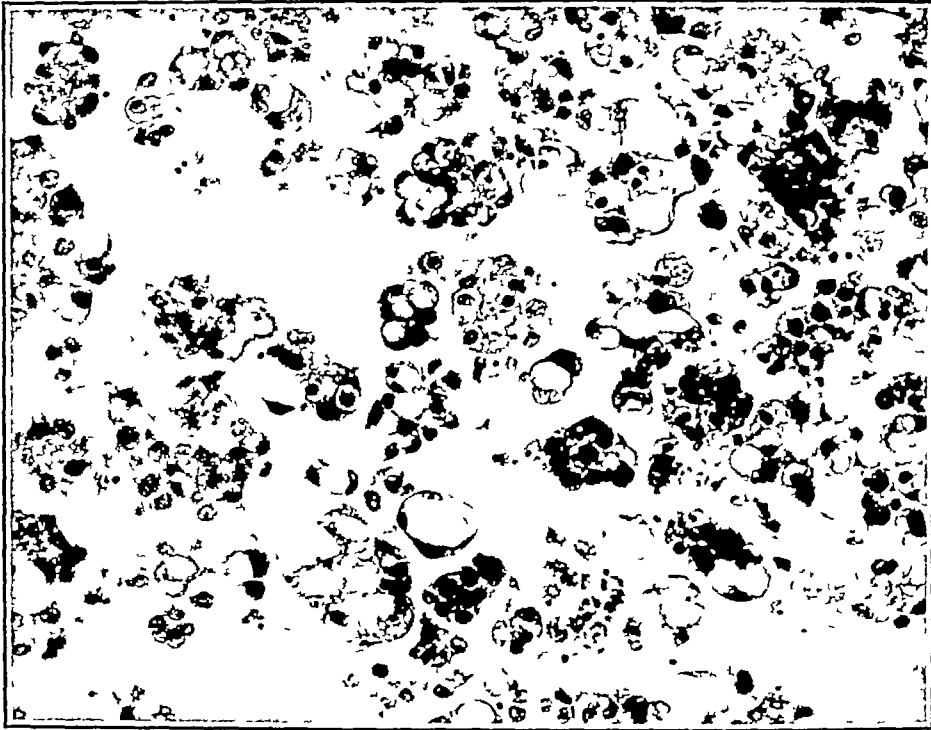


FIGURE 2 *Clumps and Crude Acini from Ascitic Fluid in a Case of Adenocarcinoma of Undetermined Origin (x260)*  
*Marked anaplasia and the presence of many signet forms are striking features*

ing is carried out as for any pathological specimen, the routine stain in this laboratory being phloxine and methylene blue.

When overnight sedimentation fails to produce a cloudy layer at the bottom of the container, we have occasionally resorted to Schlesinger's<sup>3</sup> technic of centrifuging the specimen, 50 cc at a time, pouring off the supernatant fluid and adding a fresh quantity to the same tube until the entire specimen has been centrifuged. If the fluid is too acellular to yield a good block by centrifuging alone, we employ a modification of a technic attributed by Henderson and Muirhead<sup>5</sup> to Alzheimer and originally devised for the examination of cells in spinal fluid. The method depends on the precipitation of a protein coagulum to ensnare cells suspended in the fluid. Most serous fluids contain enough protein to yield a voluminous precipitate on addition of a precipitant such as 10 per cent formalin or Zenker's fluid. The specimen is allowed to settle overnight

sheets of cells, and evidence of anaplasia in the cells composing the formation—this includes pronounced variation in nuclear staining, eccentric position of nuclei and irregularity of cytoplasmic outlines. The presence or absence of typical or atypical mitotic figures is regarded as a secondary consideration.

#### RESULTS

The records of the laboratory show that from January 1, 1931, to June 30, 1946, a total of 1078 specimens of serous fluids were submitted. Of this number, 245 were reported as yielding insufficient sediment, leaving 833 specimens actually examined. Since multiple examinations were not infrequently carried out on the same patient, the latter figure actually represents 666 patients. Qualified or unqualified diagnoses of neoplastic disease were made on one or more specimens from 102 of the 666 patients (15 per cent). C

\* owing malignancy.

nant neoplasm at autopsy or by biopsy, cell-block preparations were positive in 47 (41 per cent)

The process apparently responsible for serous effusions was found at autopsy or biopsy in 163 cases (Table 1) The types of malignant neoplasm found in this group are presented in Table 2

### DISCUSSION

The usefulness of the cell-block technic is considered to be well demonstrated by the fact that

are the care with which the cell blocks are prepared and the criteria employed in evaluating the cells found. In our relatively large series the interest in the procedure and the methods employed in the preparation of cell blocks have fluctuated from time to time. Similarly, the diagnostic criteria in use have not been constant for the entire time. Early in the period covered by this survey positive diagnoses were occasionally made on the basis of single cells, along the lines suggested by Graham<sup>6</sup>



FIGURE 3 Portion of Tumor from Pleural Fluid in a Case of Epidermoid Carcinoma of Undetermined Origin (x160)  
*Anaplastic squamous epithelial cells and several epithelial pearls are plainly seen*

positive results were obtained in 102 of the 666 patients (15 per cent) from whom fluids were with-

TABLE 1. Diagnoses Made at Autopsy or Biopsy

DIAGNOSIS	TOTAL NO. OF CASES	POSITIVE CELL BLOCK	NEGATIVE CELL BLOCK
Malignant neoplasm	114	47	67
No evidence of malignant neoplasm	49	3	46
Totals	163	50	113

drawn and submitted for examination. In Zeman-sky's<sup>2</sup> series of 730 cases positive diagnoses on the basis of examinations of cell blocks were returned in 156 cases (21 per cent). The comparable figure in the Honigsmann<sup>4</sup> study was 29 per cent, and in that of Schlesinger<sup>5</sup> was 35 per cent.

Probably the most important factors in determining the proportion of positive results obtained

More recently, there has been a tendency to increasingly conservative diagnostic standards so that at present fully formed acini and evidence of neoplastic growth in the form of individual cells are often required (Fig 1). In our opinion these criteria may safely be relaxed in certain particulars. We agree that definite cellular arrangement is essential, but a demand for complete acini is regarded as limiting the usefulness of the method. Some malignant tumors — for example, epidermoid or medullary carcinomas — may release cells that show no true acinar arrangement but are identifiable as malignant by virtue of the highly atypical cells making up the sheets (Figs 2, 3 and 4). Even in the presence of well formed acini, evidence of anaplastic cell growth should be required. Clumped mesothelial cells frequently resemble neoplastic cells (Fig 5) and may show such features as mitotic figures and binucleate forms. Such cells, however, do not have



significant irregularity in arrangement and staining of nuclear chromatin, marked variation in size of

positive diagnosis. Regarding the value of single cells in arriving at a correct diagnosis, we are in



FIGURE 4 Sheets of Anaplastic Carcinoma Cells in Pleural Fluid from a Case of Poorly Differentiated Scirrhous Carcinoma of the Breast (x220)

nuclei or gross irregularity in cytoplasmic outline. They occasionally fortuitously form cords or sheets,

agreement with Schlesinger,<sup>3</sup> who doubts whether one should ever make a flatly positive diagnosis of

TABLE 2 Malignant Neoplasms Disclosed by Biopsy or Autopsy

DIAGNOSIS	NO OF CASES YIELDING NEGATIVE CELL			NO OF CASES YIELDING POSITIVE CELL			TOTAL CASES	
	TOTAL	PLEURAL	PERITONEAL	TOTAL	PLEURAL	PERITONEAL	NO	PERCENTAGE POSITIVE
<b>Carcinoma</b>								
Bronchiogenic	18	18	0	6	6	0	24	25
Breast	6	6	0	12	12	0	18	67
Ovary	2	2	0	9	3	6	11	82
Stomach	3	1	2	3	1	2	6	50
Kidney	3	2	1	2	2	0	5	40
Biliary tract	2	1	1	2	0	2	4	—
Pancreas	1	0	1	3	0	3	4	75
Liver	2	1	1	0	0	0	2	—
Rectum	2	1	1	0	0	0	2	—
Prostate	2	2	0	0	0	0	2	—
Esophagus	0	0	0	1	1	0	1	—
Uterus	1	0	1	0	0	0	1	—
Bladder	1	0	1	0	0	0	1	—
Melanotic	1	0	1	0	0	0	1	—
<b>Sarcoma</b>								
Osteogenic	1	1	0	1	1	0	2	—
Reticulum-cell	2	2	0	0	0	0	2	—
Ewing	1	1	0	0	0	0	1	—
<b>Leukemia</b>								
Chronic myelogenous	1	1	0	0	0	0	1	—
Chronic lymphatic	1	1	0	0	0	0	1	—
Monocytic	1	1	0	0	0	0	1	—
Histiocytic	1	0	1	0	0	0	1	—
Hodgkin's granuloma	2	2	0	0	0	0	2	—
Choriocarcinoma	1	1	0	0	0	0	1	—
Teratoma	1	1	0	0	0	0	1	—
Pseudomyxoma peritonei	0	0	0	1	0	1	1	—
Lesion of undetermined type	11	3	8	7	3	4	18	38
<b>Totals</b>	<b>67</b>	<b>48</b>	<b>19</b>	<b>47</b>	<b>29</b>	<b>18</b>	<b>114</b>	<b>41</b>
<b>Average</b>								

but by rigidly demanding definite evidence of anaplasia in such cases, one can usually arrive at a

positive diagnosis on the basis of single cells, regardless of atypical features.

The large number of specimens that were reported as showing insufficient sediment for examination was undoubtedly due to the fact that suitable technics were not invariably employed. In our limited experience, we have failed to obtain sufficient sediment in only 1 case, although we have seen many specimens in which settling overnight failed to produce a cloudy layer on the bottom of the container. The application of Schlesinger's method of successively centrifuging 50-cc lots of the specimen in the same centrifuge tube or the use of a modifica-

Bronchiogenic carcinoma extends or metastasizes to the pleura, according to Honigman, in less than a third of all cases. Our finding that 25 per cent of the specimens of pleural fluids submitted on patients suffering from this type of malignant neoplasm yielded positive cell blocks thus appears not unreasonable.

The most frequent non-neoplastic causes of serous effusion in our series were heart disease (12 cases), cirrhosis of the liver (12 cases) and pulmonary or peritoneal tuberculosis (10 cases). Since tuber-

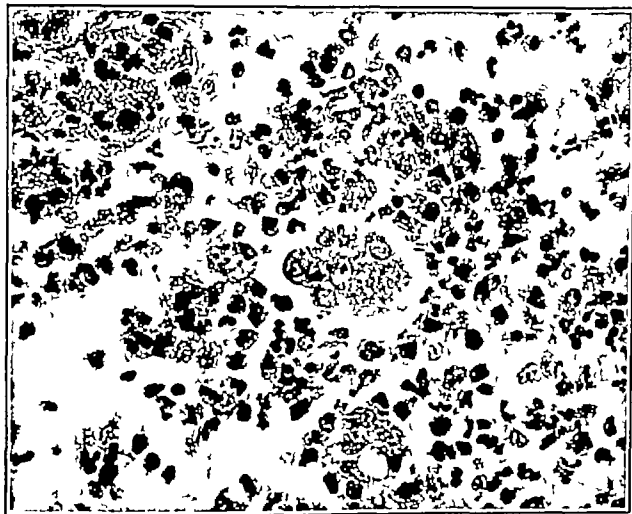


FIGURE 5 Clumped Mesothelial Cells from Ascitic Fluid in a Case of Alcoholic Cirrhosis (x560)  
The cells appear to form a crude acinus but no definite evidence of anaplasia can be made out

tion of the Alzheimer technic invariably provides sufficient sediment for examination.

Table 2 shows that positive cell blocks were most frequently seen in cases of carcinoma of the ovary, the next most frequent, in order, being carcinoma of the breast, pancreas, stomach, kidney and lung. In Schlesinger's study 100 per cent of cases of carcinoma of the ovary yielded positive cell blocks, the next most frequent types being carcinoma of the stomach, lung, colon and breast in that order. The orders in Honigman's and Zemansky's series vary somewhat from that in our own, but it is noteworthy that carcinoma of the ovary, breast, lung and gastrointestinal tract ranks well up in all the series. That carcinoma of the ovary should figure so prominently in all four studies is hardly surprising, since the tendency of the growth to produce serosal carcinomatosis and effusion is well known.

culous fluids often contain viable tubercle bacilli and are potentially infectious, proper precautions should be observed in the preparation of cell blocks from any serous effusion.

As noted in Table 1, falsely positive diagnoses were made on cell blocks from 3 cases showing no evidence of malignant neoplasm at autopsy. In 1 of these the fluid, thought to be ascitic fluid, actually was withdrawn from a large pancreatic cyst and contained well formed acini (Fig 6). These were presumably from the pancreas itself and were composed of cells showing no conclusive evidence of anaplasia. In the other cases the accumulation of ascitic fluid was apparently due to hepatic cirrhosis of long standing, and the cells thought to be neoplastic cells were actually atypical or clumped mesothelial cells (Fig 5).

significant irregularity in arrangement and staining of nuclear chromatin, marked variation in size of positive diagnosis Regarding the value of single cells in arriving at a correct diagnosis, we are in



FIGURE 4 Sheets of Anaplastic Carcinoma Cells in Pleural Fluid from a Case of Poorly Differentiated Scirrhus Carcinoma of the Breast (x220)

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Carcinoma											
Bronchiogenic	18	18	0	6	6	0	24			25	
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Ovary	2	2	0	9	3	6	11			82	
Stomach	3	1	2	3	1	2	6			50	
Kidney	3	2	1	2	2	0	5			40	
Biliary tract	2	1	1	2	0	2	4			—	
Pancreas	1	0	1	3	0	3	4			75	
Liver	2	1	1	0	0	0	2			—	
Rectum	2	1	1	0	0	0	2			—	
Prostate	2	2	0	0	0	0	2			—	
Esophagus	0	0	0	1	0	0	1			—	
Uterus	1	0	1	0	1	0	1			—	
Bladder	1	0	1	0	0	0	1			—	
Melanotic	1	0	1	0	0	0	1			—	
Sarcoma											
Osteogenic	1	1	0	1	1	0	2			—	
Reticulum-cell	2	2	0	0	0	0	2			—	
Ewing	1	1	0	0	0	0	1			—	
Leukemia											
Chronic myelogenous	1	1	0	0	0	0	1			—	
Chronic lymphatic	1	1	0	0	0	0	1			—	
Monocytic	1	1	0	0	0	0	1			—	
Histiocytic	1	0	1	0	0	0	1			—	
Hodgkin's granuloma	2	2	0	0	0	0	2			—	
Choriocarcinoma	1	1	0	0	0	0	1			—	
Teratoma	1	1	0	0	0	0	1			—	
Pseudomyxoma peritonei	0	0	0	0	0	0	1			—	
Lesion of undetermined type	11	3	8	7	3	4	18			38	
Totals	67	48	19	47	29	18	114				
Average										41	

but by rigidly demanding definite evidence of anaplasia in such cases, one can usually avoid a falsely malignant neoplasm on the basis of single cells, regardless of the presence of atypical features

## THE OCCURRENCE OF CARCINOMA OF THE THYROID GLAND IN AUTOPSY MATERIAL\*

W P VANDERLAAN, M D †

BOSTON

THERE is ample reason for confusion in attempting to interpret recent clinical and pathological reports concerning both benign and malignant neoplasms of the thyroid gland in their relation to nodular goiter. Several papers have stressed the high incidence of cancer in nodular goiter. Thus, Ward<sup>1</sup> found an incidence of 4.8 per cent, and Cole, Slaughter and Rossiter<sup>2</sup> one of 7.2 per cent. Furthermore, Hinton and Lord<sup>3</sup> observed a higher incidence of cancer in apparently benign nodular goiters (7.6 per cent) than in innocent appearing "lumps" in the breast (6.7 per cent) and therefore concluded that it is as justifiable to do a thyroidectomy for nodular goiter as a biopsy for a mass in the breast.

In view of these observations considerable interest attaches to other data indicating that nodules in thyroid glands are found at autopsy with some frequency. In a goitrous area — Chicago — Jaffé<sup>4</sup> found nodules in the thyroid glands at autopsy in 30.0 per cent of white men, 44.7 per cent of white women, 14.5 per cent of Negroes and 25.5 per cent of Negroes. Despite this high incidence of nodules, only 2 cases of carcinoma were observed in 1000 cases. On the other hand, in a nongoitrous area — Boston — Schlesinger, Gargill and Saxe<sup>5</sup> reported that 8.2 per cent of all thyroid glands examined at autopsy contained distinct nodules more than 1 cm. in diameter, and in nodular goiters from 112 cases they found 5 carcinomas (4.5 per cent) and 1 sarcoma. This higher incidence of carcinoma in nodules in the nongoitrous area may be related to the observations of Warren<sup>6</sup> that true adenomas are rarely multiple and are to be distinguished from the nodules of endemic goiter and that isolated nodules are ten times likelier to be malignant than any other type of thyroid enlargement. Thus, it might be considered that in a nongoitrous area adenomas comprise a higher proportion of thyroid nodules and hence that the percentage of carcinomas in such nodular goiters is greater than that in a goitrous area, where nodules are more frequently those of endemic goiter.

Again, however, a difficulty similar to that observed by Cole et al.,<sup>2</sup> who found 11 per cent of 100 cases of multinodular nontoxic goiter to be malignant, arises. According to Warren's view it is unlikely that these multinodular goiters were true adenomas, they appear to have been multinodular

endemic goiters. It is perhaps noteworthy that the surgical material of Cole et al. is drawn from the Chicago area, as is Jaffé's autopsy material. The application of Cole's finding that 7.2 per cent of all nodular goiters are malignant to Jaffé's figure that at autopsy nearly 30 per cent of all thyroid glands contain significant nodules means that thyroid carcinoma should be present in about 2 of every 100 cases at autopsy. Actually, Jaffé found a ratio of 2:1000.

From such considerations it seems apparent that the relation of neither neoplasia nor cancer to nodular goiter is yet clear. They serve rather to emphasize that the morphologic diagnosis of carcinoma of the thyroid gland is frequently difficult and that criteria that suffice for one pathologist are deemed insufficient by another. It seems clear, however, that the ultimate criterion for the diagnosis of cancer is that the disease naturally results in the death of the patient harboring it. It thus appeared to be of interest to review the autopsy material of the Boston City Hospital to establish the frequency with which carcinoma of the thyroid gland was found as a cause of death, for such data provide a good indication of the incidence of this disease in an unselected population. It is, of course, appreciated that any figure obtained will probably be somewhat lower than the incidence for the population as a whole, since patients of this type are rarely permitted to remain on the wards of a large general hospital, being sent home or elsewhere for the terminal stages of their disease.

The material reviewed comprised the 18,668 cases seen at autopsy in the half century from 1896 through 1945. In this period 5 cases of carcinoma of the thyroid gland occurred, in 1 it was an incidental finding at autopsy, and in 4 it was widespread and had resulted in death.

This number may be compared with those of other relatively infrequent diseases. Thus, carcinoma of the adrenal gland was more than three times more frequent, occurring in 17 cases during the same period. The incidence of primary carcinoma of the liver was much greater — 34 cases. Similarly, 30 cases of benign pituitary tumor occurred in the same period, and, in addition, there were 2 cases of carcinoma of the pituitary body. Perhaps the most striking indication of the rarity of carcinoma of the thyroid gland at autopsy is the observation that carcinoma of the duodenum, occurring in 11 cases, was twice as frequent as the former condition.

In addition to the autopsy material of the Boston City Hospital, the autopsy figures of the Peter Bent

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This work was performed under a fellowship of the American Cancer Society recommended by the Committee on Growth of the National Research Council.

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Brigham Hospital and the Massachusetts General Hospital, through the courtesy of Drs T D Kinney and Tracy B Mallory, respectively, were made available. Cancer of the thyroid gland was found to have been the cause of death in 5 cases among more than 6000 examined at autopsy at the Brigham Hospital, and the incidence of cancer of the thyroid gland was less than 1/1000 in 11,000 autopsies at the Massachusetts General Hospital. As in the Boston City Hospital series, these figures indicate a low incidence of cancer of the thyroid gland. It is of interest that in Ophuls's<sup>7</sup> series of 3000 autopsies, no thyroid cancer was found.

In view of the relative infrequency with which carcinoma of the thyroid gland has been found as a cause of death in a large autopsy experience, it seems reasonable to suggest that the pathological criteria for this diagnosis should be reviewed in cases in which microscopical examination of thyroid nodules has led to the conclusion that carcinoma of the thyroid gland is of frequent occurrence.

#### SUMMARY

In the half century from 1896 through 1945, a total of 18,668 autopsies were performed in the

Boston City Hospital, and carcinoma of the thyroid gland was found in 5 cases. Carcinoma of the adrenal gland was three times and primary carcinoma of the liver and pituitary-body tumors six times more frequent, even carcinoma of the duodenum exceeded this incidence by more than twice. At the Peter Bent Brigham Hospital and the Massachusetts General Hospital, cancer of the thyroid gland was the cause of death in less than 1/1000 cases at autopsy.

It is concluded that carcinoma of the thyroid gland is a rare cause of death.

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## CHICKEN POX WITH SIMULTANEOUS IDIOPATHIC THROMBOCYTOPENIC PURPURA\*

### Report of a Case

JEROME J COHEN, M D,† and CHARLOTTE BANSMER, M D‡

WORCESTER, MASSACHUSETTS

**C**HICKEN pox is generally considered a benign disease. The following case was accompanied by primary idiopathic hemorrhagic purpura. Since similar reported cases are few and all indicate a grave prognosis, this case is presented.

An 11-year-old boy entered the hospital because of a hemorrhagic vesicular rash, petechiae, ecchymosis, epistaxis, melena and hematuria. He had been perfectly well until 3 days before admission, when a slight fever, nausea and vomiting and headache developed. On the following day a vesicular eruption appeared on the head, face, neck and upper chest. During the next 24 hours these vesicles became hemorrhagic, petechiae, purpuric spots and ecchymoses appeared on the skin between the vesicles. The hemorrhagic areas of the skin were widespread. Bleeding from the mucous membranes was also present. Because the patient had developed slight difficulty in breathing and the hemorrhage had continued he was admitted to the hospital.

The patient was the fifth child in a family of seven. Delivery had been normal at full term, the birth weight being 12½ pounds. He had been breast fed for the first 9 months. Solid foods were added at the age of 4 months. Cod-liver oil and orange juice were given from early infancy. The patient had never presented a feeding problem. He had first walked at 14 months of age, otherwise, development had been entirely normal. At 3 years of age he suffered a minor trauma to the head, subsequently strabismus of the

right eye was noted. He had had measles, mumps and whooping cough, all in mild form. He had never had chicken pox. He had been vaccinated at the age of 6 years. There had been no operations or injuries and no previous bleeding tendencies. Progress in school had always been slow, and at the time of admission the patient was in the third grade. The other children in the family progressed normally in school. The patient had never exhibited any behavior difficulty in school, at home or at play.

The mother, who was 47 years old, had diabetes mellitus, which was treated by diet alone. She had been aware of this condition for the previous 2 years. The father, aged 47 years, was well. Both maternal grandparents had died of diabetes. Four brothers were well. An 8-year-old brother had had typical, uncomplicated chicken pox 2 weeks previously. This brother had also been vaccinated at the age of 6. Six sisters were well. There was no family history of tuberculosis, blood dyscrasias, heart or kidney disease, venereal disease or cancer.

Physical examination revealed a well developed and well nourished boy, who was co-operative and well oriented. Bright blood was oozing from both the nose and the mouth. The pupils were round, regular and equal and reacted to light and accommodation. There was a right internal strabismus, as well as large subconjunctival hemorrhages bilaterally. The right otic canal was clear, and the drum normal. The left canal showed evidence of hemorrhage, the drum could not be visualized. The tonsils and pharynx contained purplish vesicles. The tonsils were not enlarged, and there was no exudate or inflammation. The mucous membranes of the mouth contained numerous hemorrhagic vesicles. The tongue was slightly swollen, with purpuric spots scattered over the surface. The neck, chest, lungs and heart were normal.

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The abdomen was not tender and the liver and spleen were not palpable. The genitalia were normal. Examination of the rectum disclosed no masses and there was no blood on digital examination. The reflexes were normal.

There were numerous hemorrhagic vesicles, mostly on the scalp and the skin of the head, neck, upper extremities and chest (Fig. 1). There were a few such lesions on the palms of both hands and on the scrotum and penis. The vesicles were present in crops and were discrete and well demarcated.

thrombin time were normal. A blood Hinton test was negative. The albumin-globulin ratio was 1.5. All blood cultures were negative. On admission the bleeding time was 13½ hours and the clotting time 7 minutes and there was no clot retraction in 24 hours.

A diagnosis of hemorrhagic chicken pox was made on admission.

During the first 8 days in the hospital the patient had profuse epistaxis, melena and hematuria. The temperature



FIGURE 1 Photograph of the Patient Taken on the Day following Admission

Around each vesicle was a corona of subcutaneous hemorrhage that was confluent with that of the surrounding vesicles in some areas. Between the vesicles there were many petechiae and a moderate number of purpuric and ecchymotic

was essentially normal, the highest recorded being 101°F by rectum on the 2nd hospital day. He was maintained by blood and plasma transfusions, receiving eight 500-cc. transfusions in all. In addition he was given parenteral fluids,

TABLE I Pertinent Laboratory Data

DATE	RED-CELL COUNT $\times 10^4$	HEMO- GLOBIN %	WHITE CELL COUNT $\times 10^4$	NEUTRO- PHILS %	LYMBO CYTES %	MONO- CYTES %	EOSINO- PHILS %	BASOPHILS %	RETICULO- CYTES %	PLATELET COUNT $\times 10^4$
6/3	3.4	68	8.0	68	39	3	0	0	—	101
6/4	2.7	52	13.4	64	34	3	0	0	—	93
6/7	1.6	26	8.7	74	22	2	2	0	—	15
6/8	1.8	29	12.4	75	0	3	2	0	—	17
6/9	—	32	—	—	—	—	—	—	—	—
6/10	2.3	36	9.1	5	18	5	2	0	—	30
6/11	2.4	46	9.0	73	24	2	1	0	—	40
6/13	3.2	62	9.0	1	28	1	0	0	0.4	200
6/14	3.9	65	7.4	74	22	1	3	0	1	200
6/15	3.3	73	9.0	75	0	3	2	0	—	250
6/17	3.8	78	9.4	57	40	2	1	0	—	275
6/18	3.5	73	6.1	64	11	—	3	0	—	—
6/19	3.7	78	7.4	66	27	4	2	1	—	—
6/21	3.5	78	6.9	60	32	7	1	0	—	—
6/22	3.4	78	7.0	57	40	3	3	0	—	275
6/26	3.8	80	7.6	47	47	3	3	0	—	—
7/1	4.3	81	6.2	0	28	2	0	0	0.3	257
7/19	4.0	68	7.1	6	16	—	3	0	—	—
8/2	3.9	75	7.5	54	39	4	0	0	—	239
8/16	4.4	84	6.0	61	36	4	0	0	—	244
8/30	5.1	80	8.4	86	14	0	0	0	—	—

areas varying in size. A few similar lesions were present on the abdomen and the dorsal and lumbar areas as well as the lower extremities.

The pulse was 96 and the respirations 20. The blood pressure was 110/68.

The pertinent laboratory findings are presented in Table I. The blood sugar, nonprotein nitrogen, icteric index and pro-

teins and iron and ammonium citrate. Penicillin was administered intramuscularly as prophylaxis against secondary infection. The patient was in shock on two occasions during this period and responded to ordinary shock measures including oxygen therapy. A skin biopsy at the height of the disease showed chronic inflammation and hemorrhage of the dermis. On the 8th hospital day a sternal marrow puncture

performed by Dr William Dameshek was typical of idiopathic thrombocytopenic purpura

The bleeding gradually subsided, and the patient's general condition improved consistently. The skin lesions became crusted, and the crusts fell off with no residual scarring. The subcutaneous hemorrhages cleared. He was discharged on the 30th hospital day in good condition.

The patient was seen at intervals of 2 weeks for 2 months after discharge. The blood findings remained essentially normal. His general physical condition was good, with full activity. No enlargement of the spleen was noted.

In a review of the literature the incidence of hemorrhagic chicken pox was found to be extremely low.<sup>1-12</sup> The majority of cases reported do not include significant hematologic data. The clinical courses in these cases, however, closely parallel that in the case reported above except that the greater proportion terminated fatally, there being 6 deaths in the 9 cases. None of these patients were given intensive blood-replacement therapy. The cases that include hematologic data substantiate the simultaneous occurrence of idiopathic thrombocytopenic purpura.<sup>1, 2, 11, 12</sup> All the patients recovered, although in 1 case there was extensive gangrene, necessitating amputation.<sup>11</sup> In no case was there a history of a bleeding tendency or blood dyscrasia.

The case presented above, because of its symptomatology and blood findings, was deemed worthy of report in view of the severity of the symptoms. Transfusions were indicated to replace blood loss. The use of moccasin venom was considered but rejected. This venom was used in the early phase of the disease in the case reported by Stoesser and Lockwood.<sup>11</sup> Subsequent exacerbations of purpura in the same case, however, were treated by transfusions alone. The blood findings in the case presented above indicated idiopathic thrombocytopenic purpura, and this was substantiated by sternal puncture. It was believed that if the platelet count did not rise a splenectomy should be con-

sidered. The use of anticytotoxic serum was suggested by Dr Dameshek, but because of the spontaneous improvement in the platelets and general blood picture, this was not used.

### SUMMARY

A case of chicken pox with simultaneous idiopathic thrombocytopenic purpura is presented. Recovery was complete, and follow-up study showed that the patient had a normal blood picture and was in good health eight months after the acute illness.

Treatment was directed toward combating the effects of blood loss. Specific treatment of the purpura with anticytotoxic serum was considered but, because of the rapid improvement in the blood picture, was not used.

A review of the literature indicated the rarity of hemorrhagic chicken pox and its grave prognosis and suggested that all cases when investigated thoroughly from a hematologic point of view entail two entities: chicken pox and idiopathic thrombocytopenic purpura.

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## MEDICAL PROGRESS

## CURRENT CONCEPTS OF JAUNDICE, WITH PARTICULAR REFERENCE TO HEPATITIS\*

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**JAUNDICE**—or yellow staining of the skin, mucous membranes and sclerae due to the presence of excessive amounts of bilirubin in the blood—can probably be produced by as great a variety of pathologic processes as any physical finding encountered in the practice of medicine.<sup>1-4</sup> Since bilirubin is derived from hemoglobin, an understanding of the numerous mechanisms by which jaundice may develop is best approached by a review of certain aspects of the normal metabolism of hemoglobin.

## NORMAL BILE-PIGMENT METABOLISM

As shown in Figure 1, the porphyrin rings of the hemoglobin molecule are made up of four pyrrol nuclei each, the iron-porphyrin complexes being best designated as "heme." There are four heme molecules attached to each molecule of globin, but, to conserve space, only one has been shown in the illustration. Although the exact manner in which red cells are destroyed in the reticuloendothelial system is not understood, it is likely that the porphyrin ring of the liberated hemoglobin is broken at the alpha-methene bridge, iron is removed,<sup>5</sup> and the resulting iron-free compound is probably bilirubinogen, whose structural formula is demonstrated in Figure 2. According to Watson,<sup>6</sup> globin, a protein of about the same molecular weight as albumin, is attached to the pyrrol nuclei by carboxyl groups, as in the hemoglobin molecule. Bilirubinogen is transported in the blood to the liver, where bilirubin is separated from globin and excreted in the bile as sodium bilirubinate.

When bile reaches the colon, bilirubin is reduced by the bacterial flora to urobilinogen, which is a colorless compound having a structural formula like that of bilirubin except for the presence of additional hydrogen atoms. Actually, two urobilinogens (mesobilirubinogen and stercobilinogen) are formed in the bowel, but they are best referred to collectively simply as urobilinogen, since the chemical tests for

their measurement quantitate them as though they were a single compound.<sup>7</sup> Urobilinogen is readily oxidized to urobilin, an orange-yellow pigment, which is partly responsible for the color of normal stools. Inasmuch as the quantitative chemical determinations of urobilinogen involve reduction back to urobilinogen of any urobilin present, it seems reasonable to omit from most of this discussion the term urobilin as well as the confusing terms, stercobilin, stercobilinogen and mesobilirubinogen. It is adequate for the purposes of this paper to discuss hemoglobin breakdown in terms of bilirubin and urobilinogen only.

The amounts of the natural derivatives of hemoglobin that are metabolized daily in a normal person can be readily calculated. If the total blood volume is 5000 cc and the hemoglobin concentration is 15 gm per 100 cc., the quantity of circulating hemoglobin is 750 gm. The average life span of erythrocytes in normal human beings is about one hundred and twenty days, which means that 0.83 per cent of the hemoglobin mass, or 6.22 gm, is destroyed and replaced daily.<sup>8-9</sup> In normal persons destruction is thought to be confined largely to the oldest cells—that is, those about one hundred and twenty days old. Since the breakdown of 1 gm of hemoglobin results in the formation of approximately 35 mg of bilirubin,<sup>10</sup> which is excreted quantitatively,<sup>11</sup> approximately 220 mg of bilirubin is formed daily in the reticuloendothelial system and excreted into the bile by the liver. Since the molecular weight of urobilinogen is nearly the same as that of bilirubin, if all the bilirubin excreted each day is reduced in the colon to urobilinogen, approximately 220 mg of urobilinogen is formed daily.

The steps that normally lead from the destruction of red corpuscles to the excretion of urobilinogen are reviewed in Figure 3. So far as is known, the chemical changes involved take place in three sites—the reticuloendothelial system, the liver and the colon. In normal mammals most of the bile pigment is probably produced in the reticuloendothelial cells of the bone marrow, whereas the spleen and the

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In the preparation of this material no attempt has been made to include a complete review of the many controversial aspects of normal and abnormal bile-pigment metabolism. The aim has been merely to present, with illustrations, concepts that seem currently to be most acceptable and most contributory to an understanding of the pathogenesis of jaundice.

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It is likely that, when the alpha methene bridge of the porphyrin ring is removed the compound formed is verdohemoglobin, a biliverdin iron globin, which is subsequently converted to bilirubinogen.

Hawkins and Johnson<sup>12</sup> explain that it has been customary to use the equation  $40 \text{ mg of bilirubin} = 1 \text{ gm of destroyed hemoglobin}$  since the pigment radical comprises 4 per cent of the hemoglobin molecule. These authors point out, however, that bilirubin has a molecular weight of 584 and heme a molecular weight of 652, and that 1 gm of hemoglobin contains 3.35 gm of iron. On the basis of these data it is calculated that 34.9 mg of bilirubin should be derived from the destruction of 1 gm of hemoglobin. It is well to add that the quantitative conversion of heme to bilirubin, especially under pathologic conditions, is questioned by some authors,<sup>13</sup> and that much remains to be learned concerning the breakdown of hemoglobin and myoglobin to dipyrromethenes.<sup>14</sup>



Kupffer cells of the liver have a relatively minor role. Contrary to older views, the polygonal cells of the liver have only an excretory function so far

unknown. It is unlikely, however, that the pyrrol nuclei of the absorbed urobilinogen molecules are reutilized in hemoglobin formation, since pyrrol aggregates can probably be readily synthesized.<sup>11</sup> A small fraction of the absorbed urobilinogen passes through the liver to the hepatic veins, enters the

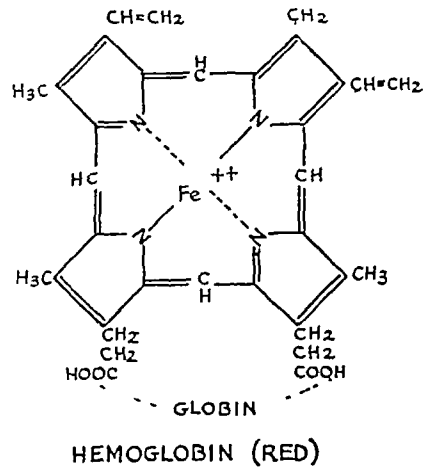


FIGURE 1 Structural Formula of Hemoglobin  
Although four heme molecules are attached to each molecule of globin, only one is shown in the illustration

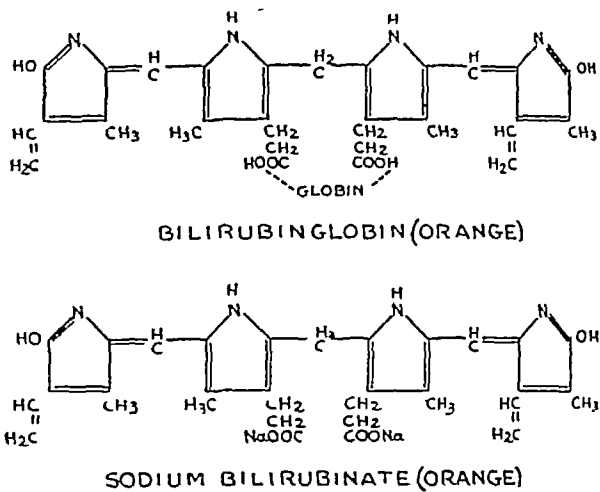


FIGURE 2 Structural Formulas of Bilirubin-globin and Sodium Bilirubinate

as bile pigment is concerned, and are not involved in the initial steps of hemoglobin breakdown.<sup>13, 14</sup> The greater part of the urobilinogen formed in

general circulation at the vena cava and is eventually excreted into the urine by the kidney. The normal range for urinary urobilinogen in adults is from

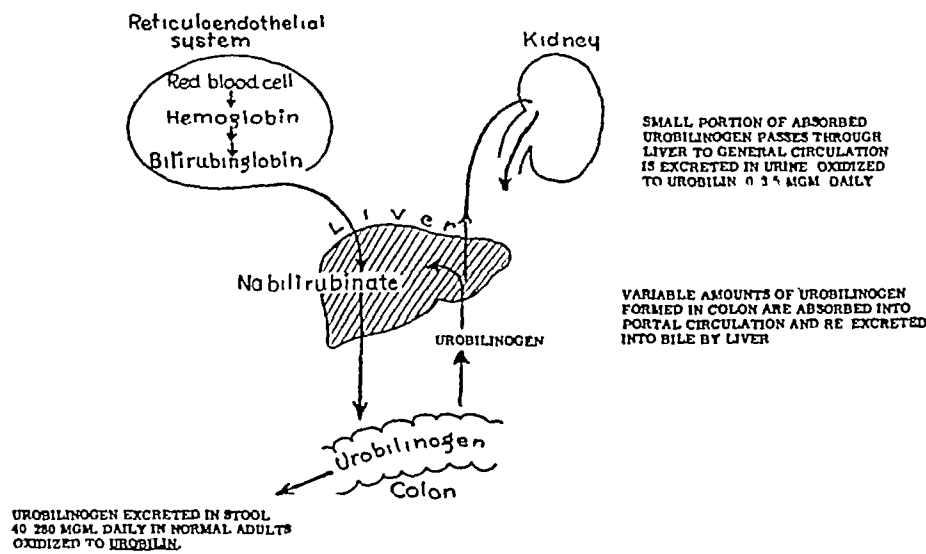


FIGURE 3 Diagram of Steps Leading from Destruction of Red Corpuscles to Excretion of Urobilinogen in Normal Subjects

the colon is ordinarily excreted in the stool, in which it is oxidized to urobilin, but a portion is reabsorbed into the portal circulation, transported back to the liver and re-excreted in the bile. The exact manner in which urobilinogen is handled by the liver is

0 to 3.5 mg a day, whereas the normal range for fecal urobilinogen is from 40 to 280 mg a day.<sup>15</sup>  
ABNORMAL BILE-PIGMENT METABOLISM  
With the basic facts concerning normal pigment metabolism in mind, the abnormalities of these

processes that are observed in the various pathologic states accompanied by jaundice may be considered Rich<sup>1</sup> has placed all the forms of jaundice in two large groups. The first type is called "retention jaundice" because bilirubin is retained in the blood

obstructive, mechanical and surgical types referred to by various authors. Although no single classification is entirely adequate, the merits of Rich's concept become apparent when the mechanisms responsible for jaundice and the clinical laboratory

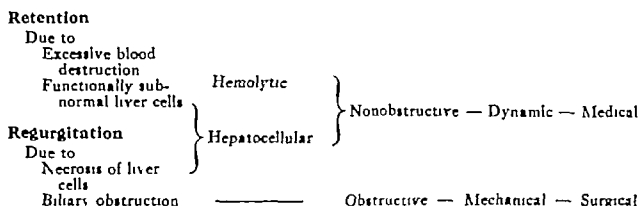


FIGURE 4 Interrelations of Various Classifications of Jaundice

owing to the inability of slightly subnormal liver cells to excrete the amounts of this pigment that are presented by the blood for clearance. The

tests used in differential diagnosis of the various forms are considered.

Figure 5, which is a modification of a drawing by Rich,<sup>1</sup> presents diagrammatically the histology of the normal liver lobule. The sinusoids lie between the cords of liver cells and carry blood from branches of the portal vein and hepatic artery to the central vein of the lobule, from which blood flows to the hepatic vein and thence to the vena cava. As blood flows through the sinusoids, certain substances, such as bilirubinglobin, are taken up by the polygonal cells and the Kupffer cells, and other substances are released from these cells to the blood. The tiny bile capillaries or canaliculi that lie between the individual polygonal cells are not ordinarily seen in sections of normal liver but are shown diagrammatically in Figure 5. The canaliculi receive freed bilirubin or sodium bilirubinate and other elements

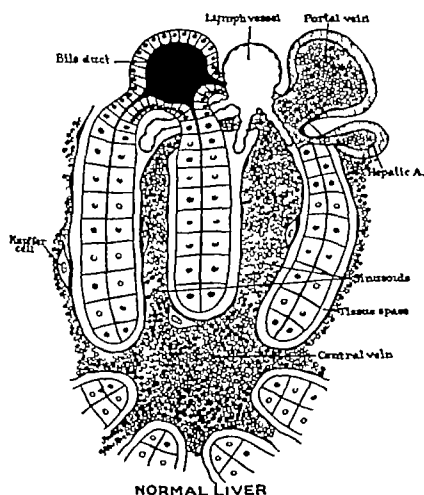


FIGURE 5 Diagram of Portion of Normal Liver Lobule (modified from Rich<sup>1</sup>)

second type is called "regurgitation jaundice" because it results from the escape or regurgitation of whole bile from the bile canaliculi into the blood stream. Retention jaundice includes the hemolytic, mild hepatocellular and nonobstructive types and dynamic or medical cases of other classifications (Fig. 4). Regurgitation jaundice, on the other hand, comprises the severe hepatocellular and the

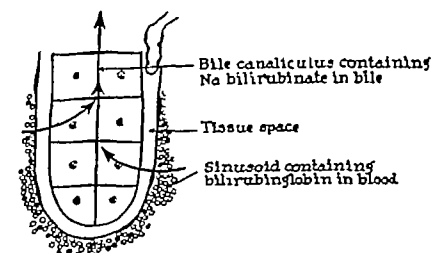


FIGURE 6 Diagram Indicating Direction of Normal Flow of Bile

of the bile from the polygonal cells and discharge them into branches of the hepatic duct located at the periphery of each lobule. The tissue spaces

between the sinusoids and the cords of liver cells are shown in exaggeration because of their importance in explaining the pathogenesis of jaundice. The supposed relation between tissue space and the lymphatic system is also apparent from this diagram.

In Figure 6, arrows indicate the direction of the normal flow of bile. Bilirubinglobin enters the polygonal cells either directly from the sinusoidal blood or via the Kupffer cells, and sodium bili-

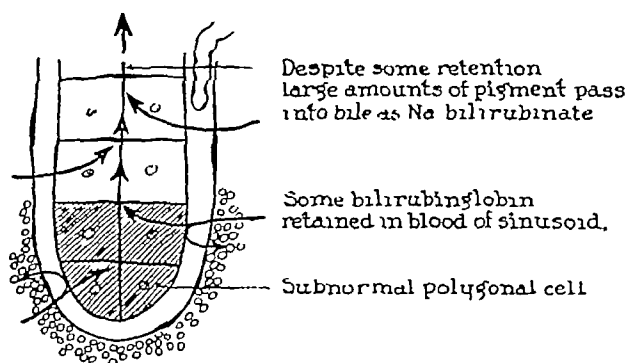


FIGURE 7 *Abnormality of Bile-Pigment Excretion in Retention Jaundice*

*Bilirubinglobin is retained in blood owing to overproduction (excessive destruction of red cells) or inability of subnormal liver cells to clear pigment, or both*

rubinate is discharged into the bile canaliculi. It is not known whether protein (probably globin) is separated from bilirubin by the Kupffer cells or by the polygonal cells,<sup>5</sup> but for the sake of simplicity, the illustrations and discussion that follow are based on the assumption that this separation is effected within the polygonal cells.

#### RETENTION JAUNDICE

Figure 7 illustrates the abnormality that is thought to be present in retention jaundice. The polygonal cells are anatomically intact, but some of them are functionally inadequate, with the result that a portion of the bilirubinglobin is refused by the cells and retained in the blood. This is particularly true in hemolytic disorders in which the rate of hemoglobin turnover may be greatly accelerated and in which tremendous quantities of bilirubinglobin are offered to the polygonal cells. The liver has an enormous reserve in its capacity to excrete bile pigment, and Rich<sup>1</sup> therefore believes that jaundice rarely develops from overproduction of pigment alone. The combination of pigment overproduction and functional impairment of polygonal cells, however, often produces jaundice.

In hemolytic anemia the liver cells may have reduced functional capacity due to anoxemia<sup>1</sup> and to the toxic effects of the products of excessive erythrocyte destruction.<sup>16-18</sup> Since these cells are

unable to excrete the excessive quantities of bilirubinglobin produced by the reticuloendothelial system, this pigment is retained in the blood and the result is clinical jaundice. Similar mechanisms may operate in pernicious anemia. In congestive heart failure the polygonal cells likewise suffer from anoxemia (stagnation and anoxic), and it seems likely that the so-called "heart-failure cells" of the lung and reticuloendothelial cells in other parts of the body break down a sufficient excess of hemoglobin from stagnated erythrocytes to burden the subnormal liver with more bilirubinglobin than can be accepted. This process is more pronounced after pulmonary infarction not only because of increased blood destruction in the lung but also because anoxemia is intensified and some substance that further impairs liver function may be elaborated in the infarct.<sup>16</sup> Retention jaundice likewise occurs in pneumonia due to anoxemia (anoxic) and to toxic insults to the liver cells in association with increased blood destruction by macrophages within the lung. Icterus neonatorum is another example of retention jaundice. The newborn infant responds to the polycythemic state by destroying large numbers of red cells during the first few days of life, and according to Rich,<sup>1</sup> the liver of the newly born is immature and apparently incapable of accepting the amounts of pigment produced. That the pathogenesis of icterus neonatorum is not entirely clear, however, is emphasized by the observations of Lin and Eastman,<sup>19</sup> who found that newborn infants excrete intravenously injected bilirubin at a normal rate.

It is now recognized that a substantial number of otherwise normal persons have an icteric index and serum bilirubin concentration that are well above the normal range, and on close inspection these people are often found to have slight icterus of the skin and scleras. If bilirubin is injected intravenously it is excreted at a relatively slow rate.<sup>20-22</sup> Although insufficient pathological studies have been made in such cases, it now seems likely that many of these subjects can be placed in one of two groups. Those with little or no evidence of hepatic or hematologic abnormality other than impaired bilirubin excretion may have what is called "constitutional hepatic dysfunction," a benign disorder that is also referred to as "familial nonhemolytic jaundice" when a familial distribution can be demonstrated.<sup>21-27</sup> It has been suggested that those with other evidence of liver disorder in addition to impaired bilirubin excretion may be suffering from the residual effects of toxic or infectious hepatitis.<sup>20, 22</sup> The natural history of the infectious variety has been clarified in recent years, and it is now appreciated that in some cases evidence of hepatitis persists for long periods after the initial attack.<sup>28-34</sup>

In constitutional hepatic dysfunction the sole defect is thought to be an inborn inferiority of otherwise normal liver cells regarding excretion of

bilirubinogen. This pigment is therefore retained in the blood in excessive amounts, even though the rate of erythrocyte destruction is normal. This is in contrast to the other examples of retention jaundice in which overproduction of pigment and diminished excretory ability of the liver combine to produce the icteric state. Further study will be necessary to determine the extent to which some cases of mild hepatitis and some cases of late con-

chronic hepatitis and cirrhosis has, however, been appreciated only in recent years.<sup>22-23</sup> An understanding of the etiology and pathogenesis of infectious hepatitis and serum hepatitis has been reached even more recently. Investigations of hepatitis were, in fact, among the major contributions of military medicine during World War II and are therefore given separate consideration below.

#### *Due to Biliary Obstruction*

Because of the liver's enormous reserve, jaundice does not ordinarily result from biliary obstruction unless the flow of bile through the major part of the duct system is prevented.<sup>1</sup> When this occurs, the ducts and canaliculi are overfilled with bile (Fig 9), the tips of the canaliculi bulge into the tissue space, and bile diffuses into this space and thence to the lymphatic vessels and to the general circulation via the thoracic duct.<sup>40-41</sup> The ampullae that connect the bile capillaries with the smallest bile ducts or canals at the periphery of the lobule

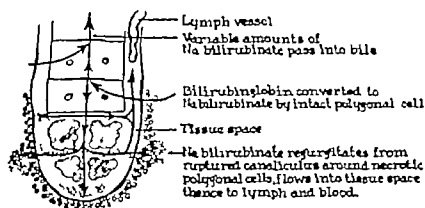


FIGURE 8 Mechanism of Regurgitation of Sodium Bilirubinate (and Other Bile Constituents) in the Presence of Hepatocellular Necrosis (after Rich)<sup>1</sup>

valescent and chronic hepatitis may be considered instances of retention jaundice. It is pointed out below that typical bouts of acute hepatitis are examples of regurgitation jaundice.

#### REGURGITATION JAUNDICE

##### *Due to Necrosis of Liver Cells*

As stated above, regurgitation jaundice is due to a reflux of whole bile from the canaliculi into the blood stream. Figure 8, which illustrates the concept of Rich,<sup>1</sup> indicates that when some of the liver cells are necrotic, the adjacent bile canaliculi are no longer intact. Bilirubinogen passes through the remaining liver cells and is converted to sodium bilirubinate in the usual way, but a large portion of the freed bilirubin regurgitates around the necrotic cells and into the tissue space, entering the blood via the lymphatic system and perhaps also by diffusion into the sinusoids. Such a mechanism operates in many cases of hepatocellular necrosis regardless of etiology.\*

Many of the causes of extensive liver-cell damage have been known to the medical profession for some time. Among these are chemical agents, such as chloroform, carbon tetrachloride, cinchophen and arsenamine, infectious agents, such as the virus of yellow fever and the spirochetes of syphilis and Weil's disease, and metabolic disturbances, such as those that are thought to occur in eclampsia. The role of dietary deficiency in the pathogenesis of

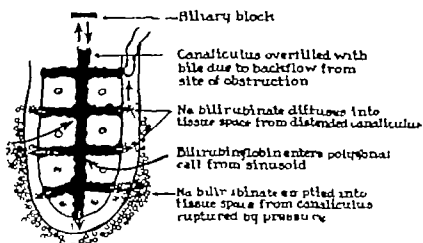


FIGURE 9 Mechanism of Regurgitation of Sodium Bilirubinate (and Other Bile Constituents) in the Presence of Biliary Obstruction (after Rich)<sup>1</sup>

may act as safety valves by rupturing and thus reducing back pressure on the liver cells.<sup>42</sup> When pressure in the bile capillaries rises sufficiently, however, the capillaries rupture, and whole bile regurgitates freely into the tissue space, entering the blood stream via the lymphatic vessels and perhaps by diffusion directly into the sinusoids.

Most of the causes of extrahepatic biliary obstruction, such as tumor, stone and stricture, are well known and require no comment. The exact nature of so-called "intrahepatic obstructive jaundice,"<sup>43-44</sup> on the other hand, is not well understood. Laboratory evidence of partial—and sometimes complete—biliary obstruction has been found in cases of hepatitis due to a variety of causes and with variable amounts of associated hepatocellular damage. Steigmann and Popper<sup>44</sup> emphasize the fact that in these cases the bile capillaries are dilated, whereas the larger ramifications of the biliary system beyond the ampullae are actually

\* Watson<sup>1</sup> considers it possible that in regurgitation jaundice globin is removed by the Kupfer cells, after which bilirubin is released by the polygonal cells and returns to the blood via the lymphatic vessels or possibly by direct diffusion into the sinusoids.

narrow. It is therefore held that obstruction must be present in the vulnerable ampullae that join the tiny bile capillaries with the smallest—variously named—bile ducts. It is thought that exudate may compress the ampullae, and that in some cases fibrous tissue may replace the exudate, causing the fixed obstruction of chronic hepatitis or cirrhosis. Bile plugs or thrombi, swelling of the liver-cell cords and edema formation in the tissue spaces surrounding the cords and the ampullae have also been suggested as causes of intrahepatic obstructive jaundice.

There is considerable difficulty in assessing the histologic findings in these cases, but further studies

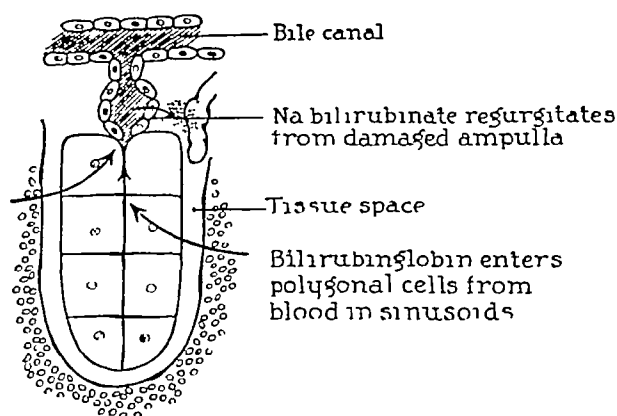


FIGURE 10 Mechanism of Regurgitation of Sodium Bilirubinate in the Presence of Cholangiolitis (modified from Watson<sup>5</sup>)

of autopsy material and of trocar aspiration biopsies of the liver obtained during different phases of hepatitis should serve to clarify the mechanisms of intrahepatic obstruction. In a personal communication Drs. Chester M. Jones and Wade Volwiler stated that, on the basis of recent, extensive observations, aspiration biopsy makes it possible to differentiate clearly jaundice due to hepatitis and that due to an otherwise silent or undiagnosed extrahepatic block. These investigators also emphasize the fact that properly prepared aspiration biopsies, when used in conjunction with laboratory tests, often enable the clinician to evaluate the phase of hepatitis with which he is dealing.

#### Due to Cholangiolitis

Watson and Hoffbauer<sup>34</sup> are of the opinion that in some cases of hepatitis, particularly those of the chronic type, regurgitation jaundice may be due chiefly to increased permeability of the cholangioles. According to their concept, which is illustrated in Figure 10, sodium bilirubinate escapes into the tissue space from the injured ampullae of the bile capillaries and presumably re-enters the blood via the lymphatic vessels or by diffusion into the

sinusoids. Since relatively more water and less solid matter would be expected to leak from the damaged ampullae, it is assumed that the bile remaining in the intralobular canaliculi tends to become inspissated, thus promoting the formation of bile thrombi. In some of the cases studied by Watson and Hoffbauer, however, bile thrombi were not conspicuous. Impressive evidence of other reputed causes of intrahepatic biliary obstruction, such as periportal cellular infiltration and swelling of liver-cell cords, was also lacking in their cases.

Regurgitation jaundice, regardless of its cause, is characterized by the escape into the circulation of bile salts and other constituents of the bile in addition to bilirubin. Accumulation of bile salts in the blood is considered a possible cause of pruritus—a symptom that is prominent in many cases of regurgitation jaundice, particularly those due to extrahepatic biliary obstruction, but is almost uniformly absent in retention jaundice. It should also be emphasized that in regurgitation jaundice, the bilirubin that re-enters the blood has been separated from globin by passage through the liver cells. Regurgitated bilirubin, perhaps because it is in the form of sodium bilirubinate, does not recombine with globin in the circulation<sup>5</sup>; it therefore readily passes the renal filter and also gives a direct van den Bergh reaction, as explained below.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., Editor

BENJAMIN CASTLEMAN, M.D., Associate Editor

EDITH E. PARRIS, Assistant Editor

### CASE 33331

#### PRESENTATION OF CASE

A fifty-five-year-old housewife entered the hospital because of jaundice.

Seven years before entry the patient had had an attack of jaundice and pain in the right upper quadrant. She was hospitalized for two weeks, during which time a Graham test showed no gallbladder shadow. The symptoms disappeared, and bladder shadow. The symptoms disappeared, and surgery was refused by the patient. For the past four years, and especially for the past seven months, the patient had lacked energy, had become easily fatigued and had considerable malaise. During the three weeks before entry she had been jaundiced and had noted dark urine, but she was vague about the color of the stools. No pruritus had been present. Small red spots had been noted on the arms. The appetite had completely disappeared. There had been no chills, fever, pain, nausea, vomiting or definite melena, although the stools were oc-

asionally dark. The diet was fat-free and low in protein. The patient said that she drank eight or nine small glasses of sherry and a little whisky each week.

Examination showed a markedly jaundiced, alert woman in no acute discomfort. There were numerous spider telangiectases over the thorax and arms. The abdomen was tense, with dullness in the flanks. The liver edge was palpable 6 cm. below the costal margin.

The temperature was 100.8°F., the pulse 85, and the respirations 18. The blood pressure was 125 systolic, 80 diastolic.

Examination of the blood showed a red-cell count of 3,600,000, with 12 gm of hemoglobin, and a white-cell count of 18,500, with 82 per cent neutrophils. The urine gave a ++ test for albumin and a +++ test for bile, there was no sugar, and an essentially normal sediment. The stools were brown and guaiac negative. The stool urobilinogen was half that of a control. The prothrombin time was 18 seconds (normal, 15 seconds). A van den Bergh reaction was 18.4 mg direct and 23.7 mg indirect. The nonprotein nitrogen was 23 mg per 100 cc., and the amylase, 24 units per 100 cc. The phosphorus was 2.4 mg, the alkaline phosphatase 16.2 units, the cholesterol 187 mg and the cholesterol esters 99 mg per 100 cc., the total protein was 5.9 gm per 100 cc., the albumin being 2.9 gm and the globulin 3.0 gm, an albumin-globulin ratio of 0.97. A blood Hinton reaction was negative. A cephalin-flocculation test was + in twenty-four hours and ++ in forty-eight hours.

A barium enema and chest films showed no abnormalities. A gastrointestinal series

large diverticulum arising from the second portion of the duodenum that could have been a barium-filled gall bladder. There was a fistulous tract from the second portion of the duodenum to the biliary tree (Fig 1). Whether this was regurgitation through the ampulla or through a biliary fistula was not ascertained.

The patient's hospital course was unsatisfactory. A high protein and vitamin intake was maintained by mouth and by use of a stomach tube and intra-

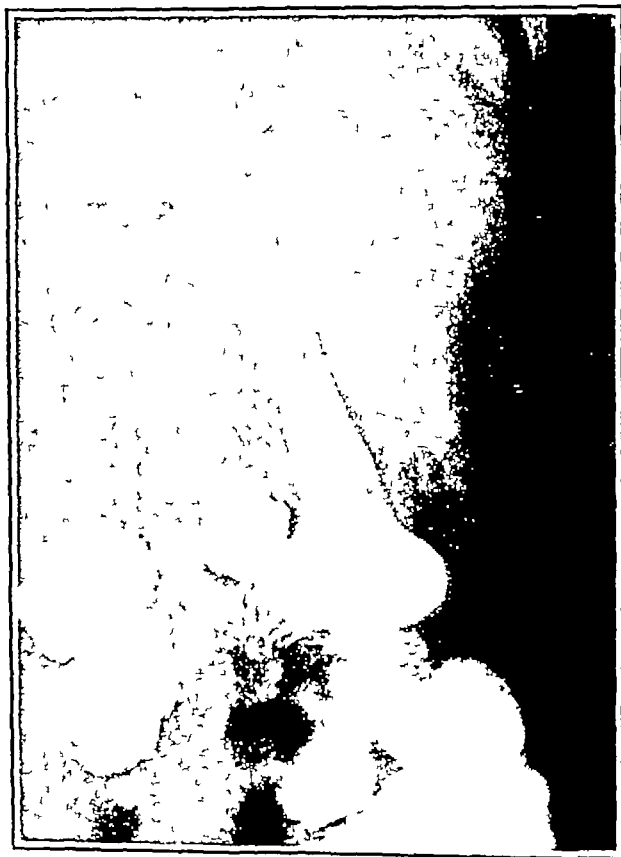


FIGURE 1 *Barium-Filled Stomach and Duodenum*  
*Barium is seen to ascend into the biliary tree — probably the common duct*

venous injections. The appetite remained poor. On the seventh hospital day the urine sediment contained numerous white cells, and the albumin rose to + + + +, no casts were seen, and a culture revealed colon bacilli. Three days later the white-cell count was 35,400. Streptomycin and penicillin were administered. The amount of albumin and the number of white cells in the urine diminished. Injections of Intrahepatol were given daily from the seventh to the thirteenth hospital day. Two transfusions were given without reaction. The patient became comatose on the twelfth hospital day, developed muscular twitching and incontinence of urine and feces and died on the eighteenth hospital day.

## DIFFERENTIAL DIAGNOSIS

DR BERNARD M JACOBSON It is to be noted that although this patient had been ill for the past four years and especially during the past seven months, the jaundice was noted only about three weeks before entry. The statement is made that the abdomen was tense, with dullness in the flanks. We are not told about the presence of shifting dullness or fluid wave, and we therefore have no certain evidence of the presence of ascites. The liver edge was noted to be palpable 6 cm below the costal margin. I should certainly like to know where the upper border was percussed and what the edge was like. A liver edge felt 6 cm below the costal margin in a person whose upper border is percussed in the seventh space is compatible with a ptotic liver rather than a large liver. The blood findings were essentially those of a normocytic and normochromic anemia. The fact that the stools were brown rules out complete obstruction of the common bile duct. The presence of a biphasic van den Bergh reaction suggests diffuse liver-cell damage. The serum amylase of 24 units is not high enough to indicate pancreatitis. The high alkaline phosphatase was undoubtedly due to the jaundice. The cephalin-flocculation test also indicates diffuse hepatic derangement. A serum cholesterol level of 187 mg and a cholesterol ester level of 99 mg constitute a fairly normal ratio, if the cholesterol esters were markedly lowered in relation to the total cholesterol, the presence of severe liver-cell dysfunction would be indicated. The serum albumin was obviously low. This change could have been due either to diffuse hepatic disease or to poor protein intake, as suggested in the history. The results of the gastrointestinal x-ray studies leave me undecided about the presence of a cholecystoduodenal fistula. It is unfortunate that this point remains in doubt, for the presence of such a fistula would furnish strong evidence for a gall-bladder calculus. We are later told that the patient developed a urinary-tract infection, which undoubtedly was a terminal cystitis and possibly a pyelonephritis. I do not know what Intrahepatol is, but I presume that it is some form of crude liver extract. During the last six days of the patient's hospital stay, she was obviously suffering from acute liver failure. We have no clinical or chemical evidence that this terminal state was due to renal failure. In summary then, this patient undoubtedly died in terminal acute hepatic failure after a long siege of derangement of function of the liver or of the biliary tract or of both organs.

In view of the history of seven years of undoubted cholelithiasis with common-duct obstruction and of the possible presence of a cholecystoduodenal fistula, I am seriously thinking of obstructive biliary cirrhosis as the likeliest diagnosis. In keeping with this possibility are the facts that there was present only a moderate degree of liver enlargement and that

the jaundice appeared to be out of proportion to the size of the liver, in comparison, for example, with what might obtain in portal cirrhosis. The next likeliest possibility to explain the entire picture is portal cirrhosis. Against this diagnosis, however, is the fact that several characteristic findings are lacking. Thus, there is no obvious history of an excessive intake of alcohol or of hematemesis, there were no dilated veins over the chest and abdomen, no esophageal varices were noted in the gastro-intestinal x-ray films, and the spleen is not described as enlarged. It is true, however, that none of the foregoing observations eliminate the possibility of portal cirrhosis. The age of the patient and the only slight enlargement of the liver, to my mind, furnish no evidence for biliary cirrhosis. Carcinoma, however, of either the liver, the biliary tree or the head of the pancreas cannot be lightly dismissed. Cancer in these locations is missed all too often in preoperative diagnoses. There is nothing in this patient's course that helps rule out carcinoma of the biliary tree or secondary carcinomatosis of the liver, but for the latter we have no knowledge of a primary source. There is no mention of a palpably large gall bladder, the obstructive jaundice was obviously not complete, and there was no x-ray evidence of compression of the duodenum, since these three points are lacking, the diagnosis of carcinoma of the head of the pancreas is unlikely. Finally, against the diagnosis of carcinoma is the long duration of the illness, if we assume that the patient had been suffering from the present illness for about four years.

I believe that the diagnoses that best fit the entire picture are obstructive biliary cirrhosis, due to calculus disease, and terminal acute hepatitis.

DR MILFORD D. SCHULZ. The film of the visualized upper gastrointestinal tract shows an essentially normal stomach and duodenum. There must be a communication between the biliary system and the duodenum, for barium is seen to ascend into the biliary tree, but whether by way of a patulous ampulla or by way of a cholecystoduodenal fistula is not evident. The irregular collection of barium seen above the duodenal loop is probably a diverticulum of the duodenum but could conceivably be a barium-filled gall bladder, although it is in a rather unusual position. No varices are evident.

DR WADE VOLWILER. Many of us who saw the patient were inclined to consider a dual etiology of the fatal liver disease. The jaundice and the right-upper-quadrant abdominal pain seven years previously, coupled with the probable choledochoduodenal fistula, strongly suggested previous common-duct stones. It seems reasonable that some degree of biliary cirrhosis could have resulted from a relatively silent long-standing partial common-duct obstruction of a degree insufficient to produce continuous jaundice. The liver was large and firm. The amount of liver damage clinically present, however, seemed greater than what could be accounted

for on the basis of this simple explanation. There was, indeed, a rather impressive story of dietary inadequacy, which suggested that fatty infiltration of the liver from malnutrition and a mild but steady intake of alcohol was also present.

I thought that liver failure from the combination of these two distinct types of liver disease was precipitated by an acute exacerbation of bacterial cholangitis, which would explain the marked leukocytosis.

The liver-function tests did not help in the diagnosis. The cephalin-flocculation test was within the limits of normal. In this hospital the cholesterol-cholesterol ester ratio has proved to be extremely unreliable in confirming the presence or absence of parenchymatous liver disease.

The patient was treated intensively with food, whole-blood transfusions and antibiotics and was too ill for any truly definitive diagnostic procedures, such as liver biopsy.

#### CLINICAL DIAGNOSIS

Biliary cirrhosis, with cholemia

DR JACOBSON'S DIAGNOSES

Obstructive biliary cirrhosis

Terminal acute hepatitis

#### ANATOMICAL DIAGNOSIS

*Acute cirrhosis of liver, alcoholic type*

Dilatation of ampulla of Vater, with regurgitation of duodenal contents into bile ducts and gall bladder

Bile nephrosis

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY. I am a confirmed skeptic regarding histories of alcoholism. A man's history should probably be doubled, a woman's tripled or quadrupled, and a teetotaler's discredited entirely. This woman died of acute portal cirrhosis of the liver of the type we ordinarily call "alcoholic," although most of us believe that alcohol is only indirectly responsible and that protein deficiency is the immediate cause of the liver injury. The liver was large, smooth, fatty, deeply bile stained and of slightly increased consistence. Microscopical examination showed marked fat vacuolization, many necrobiotic liver cells and the characteristic hyaline degeneration of the type that my father, Dr. Frank B. Mallory, described as pathognomonic for this type of cirrhotic process. Further evidence of the acutely progressive character of the lesion was the infiltration of the tissues, both lobular and interlobular, with polymorphonuclear leukocytes. There was moderate proliferation of fibrous tissue, which tended to invade the lobules. The intrahepatic bile ducts were quite normal and showed neither proliferation nor inflammatory changes.



There was no fistulous connection between the biliary tract and small bowel, but the mouth of the common bile duct at the papilla was widely patulous and intestinal content was found in the common duct and gall bladder. The duct was dilated, but the gall bladder was of normal size, without evidence of inflammatory reaction. There were no stones. The spleen was moderately enlarged, weighing 370 gm, and the veins in the lower third of the esophagus were prominent but not demonstrably varicose. We found no pyelonephritis or cystitis, but the kidneys were somewhat swollen and showed microscopically a moderately severe grade of bile nephrosis.

### CASE 33332

#### PRESENTATION OF CASE

A sixty-five-year-old man entered the hospital because of a mass in the lower abdomen.

Five years before admission the patient first noted decrease in the caliber of the stools. About three years before admission he had an ache and constant feeling of tiredness in the lower back. These symptoms became progressively worse. Three years before admission the abdomen was explored at an outside hospital, and a mass was found in the left lower quadrant. Excessive bleeding limited the operation to a biopsy, which was reported as showing "hemangioma." A positive blood Hinton test was found at that time, and the patient was treated with arsenic and bismuth for a period of nine months. Following operation the left leg became swollen, weak and tender. The patient slowly recovered, although weakness and numbness continued to bother him and the leg occasionally became swollen. During the hospital stay he lost an estimated 35 pounds in weight, which he never regained. During the three years before admission to this hospital the patient became progressively weaker, the mass steadily larger, and the constipation increasingly severer and just prior to admission he began to experience urgency, with a nocturia of one or two times, and a weakening of the urinary stream, without dysuria, hematuria or other genitourinary symptoms. The stools were never bloody or dark in color, and there was never more than minimal abdominal pain associated with bowel movements or otherwise. A thin, colorless "jelly-like" material was occasionally passed by rectum.

Physical examination showed a well developed but rather poorly nourished man. There was a definite bismuth line along the lower incisors. The heart and lungs were not remarkable. On examination of the abdomen a rounded, symmetrical protuberance was easily visible in the suprapubic area. It was firm, smooth and slightly tender, the upper limits could be easily outlined just below the umbilicus, but the lateral margins converged inferiorly. A soft, ballotable mass, which disappeared after voiding, was felt anterior to the large solid mass.

The rectum was narrowed and displaced to the right side of the pelvis by a lobulated portion of the mass that seemed to be firmly attached in the iliac fossa. No prostatic tissue could be felt on either side. The left leg showed moderate pitting edema to the knee. There was difficulty in dorsiflexing the left foot above a right angle, which was attributed to a tense Achilles tendon and not to weakness of the muscles of dorsiflexion. There was slight weakness of the psoas and quadriceps muscles on the left, but no reflex changes and no changes in sensation.

The red-cell count, white-cell count and hemoglobin were normal. The urine showed an occasional red cell, 4 or 5 white cells and an occasional granular and hyaline cast per high-power field. A stool gave a positive guaiac test. Blood Hinton and echinococcus skin tests were not reported. The nonprotein nitrogen was 37 mg and the total protein 7.2 gm per 100 cc, the chloride was 108 milliequiv per liter. The prothrombin time was 25 seconds (normal, 19 to 20 seconds). An x-ray film of the chest was normal. An intravenous pyelogram was unremarkable except for lateral displacement by the mass of the lower third of each ureter. There was no dilatation of the ureters or pelves, although no dye was seen in the bladder after twenty minutes. No involvement of the bony pelvis could be demonstrated. A barium enema showed marked displacement of the rectum and sigmoid to the right side of the pelvis (Fig 1), the latter being also pushed upward and, in its upper part, giving the appearance of attachment to the mass, elsewhere it was movable. On a post-evacuation film the greatest amount of the barium remained in the colon.

On the tenth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR EDWARD HAMLIN, JR. It seems to me that the problem here should be narrowed down to deciding what sort of mass was in the pelvis. If so, there are many possibilities. I hope that the x-ray films will be helpful.

DR STANLEY M. WYMAN. I should not call the lungs normal. Although the films were taken with the patient lying on his back, the hilar vascular shadows are more prominent than usual. I believe that there is considerable collapse of one or both lower lobes, which possibly suggests congestion and some atelectasis. An additional fact that may help is that this film, taken elsewhere three years previously, shows the rectum displaced to the right, with the sigmoid running over the mass. Our film shows that the mass is considerably larger.

DR HAMLIN. Is there any calcification?

DR WYMAN. I see no calcification in the mass.

DR HAMLIN. They are fascinating pictures but not particularly helpful. It seems from the appearance of the x-ray films that the mass lies retroperitoneally, otherwise it would not displace the

ureters and rectosigmoid to such an extent. So I shall limit myself to a discussion of retroperitoneal masses

Was this a malignant or a benign tumor? There is little evidence to suggest that it was malignant. It might have been a malignant tumor in the sense that it would be locally recurrent when excised, but in the ordinary sense of invasive or metastasizing potentialities, the evidence is nil. So let us narrow ourselves down to the consideration of benign retroperitoneal tumors. By the way, was the patient proctoscoped?

Dr TRACY B MALLORY There was a note that they tried but were unsuccessful.

Dr HAMLIN I can well see why they could not.

We already have a positive diagnosis of hemangioma, and whether that is in the nature of a red herring or whether we are supposed to think that it is a red herring, I do not know. It is difficult to eliminate it entirely. We have evidence for a vascular tumor because the surgeon who operated backed out. It is possible that in the original operation some damage was done to the left iliac vessels, following which the patient had edema and some weakness of the left leg, although that is difficult to interpret.

There was a positive blood Hinton test. I have never heard of gumma of such a nature, and since I have never heard of it, I shall not discuss it further.

Someone did an echinococcus skin test, the results of which are not recorded. That sounds like another red herring because the evidence is so slim and also because a primary retroperitoneal echinococcus lesion is rare. I shall dismiss it.

Dr JOSEPH C AUB Where did the patient come from?

Dr MALLORY New Hampshire

Dr HAMLIN Not a typical geographic location for echinococcus disease.

It simply comes down to my reciting the list of relatively benign retroperitoneal tumors and picking out one and saying, "That is it," because I have so little information that will give me any help, except the one thing that I have mentioned, namely, that it was vascular. Generally speaking, benign tumors are not vascular. I doubt that this was hemangioma. It is extremely unusual for such a tumor to produce a space-occupying mass of this size. It was also said to have been lobulated. Most of these tumors are lobulated. It conceivably could have arisen from the sigmoid, but the evidence for that is meager indeed. If it did arise in the sigmoid, one would postulate a leiomyoma, a neurofibroma or something of that nature. Chordoma may be found in that area, but no bony abnormality is recorded, and it is inconceivable that such a lesion could exist without bony abnormality. Then there are the fibromas, the myxomas and the lipomas. A lipoma of that size should be radiotranslucent, so I shall eliminate lipoma.

This is a rather typical place for enchondroma. The tumor was fixed. I should have expected that an enchondroma of this size would have shown calcification. The vascularity of the lesion is not explained by enchondroma.

There are a great many rare tumors, the gangliogliomas and so forth, but I doubt that any such tumor was found.

I am backed up to the wall here because I have no more leads for one type of tumor than for another.



FIGURE 1

Because enchondromas do exist in the pelvis, are lobulated and firm, and often displace viscera, as do lesions of these other types, to be sure, I shall "stick my neck out" and call it an enchondroma.

Dr MALLORY Are there any suggestions?

Dr GORDON A DONALDSON Could it be a meningocele?

Dr MALLORY This is the region for a meningocele, but I think that the X-ray Department would have had something to show if that were the case.

Dr WYMAN There is no evidence of spina bifida.

#### CLINICAL DIAGNOSIS

Retroperitoneal neurofibroma

#### Dr HAMLIN'S DIAGNOSIS

Sacral enchondroma

## ANATOMICAL DIAGNOSIS

*Retroperitoneal neurofibrosarcoma*

## PATHOLOGICAL DISCUSSION

DR MALLORY Dr Hamlin was skeptical of the previous biopsy report of hemangioma, and I think justly so. This would be an odd location for a huge hemangioma. My guess is that at the first biopsy only the capsule of the tumor was removed, which probably contained large vessels that suggested hemangioma. It is possible, however, that they actually got into the tumor and made that diagnosis. It sometimes is difficult to differentiate a scirrhus type of angioma and a vascular type of fibroma.

The tumor that Dr Carroll B. Miller resected was a large one, measuring 20 by 10 cm, and was adherent to all the retroperitoneal structures. Histologically it was a fibrous tumor of moderate cellularity, and we called it a low-grade neurofibrosarcoma, just on the borderline of malignancy from the histologic point of view. It was necessary in removing it to jeopardize the blood supply of the sigmoid, so that a resection of that had to be done, but it did prove possible to enucleate the tumor.

Another possibility in this area is a giant follicular lymphoma. We see a few cases with durations as long or very nearly as long as this, and these tumors are prone to arise in the retroperitoneal tissues.

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## MEDICAL CARE FOR VETERANS

AT LONG last the labors of the special committee created by the Council of the Massachusetts Medical Society to deal with the medical care of veterans seem about to bear fruit. Published elsewhere in this issue of the *Journal* is the new contract, acceptable to both the Society and the Veterans Administration, under which the members of the Society who wish to participate may do so under a so-called "gentlemen's agreement."

The efforts to achieve this end have been involved rather than long in point of time. At its meeting on February 6, 1946, the Council, at the request of General Hawley, appointed a special committee to deal with the problem of the medical care of veterans and their dependents. Two plans were in

existence at that time. The plan in operation in Michigan represented an example of the first. Under this plan the Michigan Medical Service acted as agent, paying the doctors according to an accepted fee schedule, and collecting from the Veterans Administration. According to the second—the Kansas plan—the state medical society submitted to the Veterans Administration a list of members who wished to work under an established fee schedule according to a "gentlemen's agreement."

The committee agreed on the first type of plan for Massachusetts, and it was adopted at a special meeting of the Council on April 10, the Blue Shield to act as intermediary agent. The Executive Committee of the Council was empowered to give final approval to any contract involving the Massachusetts Medical Society, and a fee schedule drawn up by the committee was accepted at that meeting.

At the October 2 meeting of the Council, the report of the committee indicated that in order to co-operate with the Veterans Administration the Society must differentiate specialists and non-specialists. This had never been done, but after much discussion the Council swallowed hard and agreed that specialists could be named "for the purposes of the Veterans Administration only."

The Executive Committee, at the same meeting, recommended that the Council rescind the vote designating the Blue Shield as administrative agent for a veterans' medical-care plan in Massachusetts, on account of certain distressing difficulties encountered in New Jersey. The whole matter, however, was tabled, and the plan as agreed on was continued up to the moment of the Executive Committee meeting of April 23, 1947. Since it was then made apparent that the Blue Shield had failed to obtain necessary legislative approval for the contract, the whole matter was reopened, and at the meeting of the Council on May 19, the committee was instructed to enter into negotiations with the Veterans Administration for a contract along the lines of the Kansas plan. It is this new contract that is presented elsewhere for perusal.

According to this plan, briefly, the Society requests its members to participate in a program whereby physicians in private practice in the Commonwealth will render medical services in such

cases as may be authorized by the Veterans Administration. Fees will be paid to the physician by the Veterans Administration according to an established fee schedule, although no physician will be permitted to accept fee-basis cases in excess of a total compensation of \$6000 in any one year without prior approval of the Administration.

The Massachusetts Medical Society will submit lists of participating members, properly broken down according to geographic distribution, and will assist the Veterans Administration in establishing a list of competent specialists who meet the qualifications of a specialist according to the regulation of the Administration.

Let us hope that this new plan will meet with the success merited by the hard work that Dr. Humphrey L. McCarthy and his committee have put into it.

### PEDIATRIC SURVEY FIRST FRUITS

THE countrywide study of child-health services inaugurated by the American Academy of Pediatrics in 1944 and now entering on its last lap has been truly a pioneer effort. Never before has a great division of medical practice sought objectively to analyze its own beliefs and its prejudices, its achievements and its failures, and its opportunities. If, in the final analysis, this effort seems to have been productive, others will surely follow.

One thing is certain. This survey cannot be compared to a grand spring housecleaning, where the windows are washed and the corners swept and then the brooms are put away in the closet. It is the setting in motion of a train of constructive ideas, of which those of permanent value will be put into operation at different times and in different places according to local needs and to the degree of local progressiveness. If this study has been soundly conducted, — and of that there is every reason to be certain, — its data will continue to be studied and its recommendations adopted a dozen years from now.

The study in Massachusetts has been completed, thanks to the untiring efforts of the state chairman, Dr. James M. Baty. The figures, which were obtained as a result of a high degree of professional co-operation, will not be correlated and published,

however, until late in the fall. One deduction seems justified even at this early date and might be entertained as a provisional conclusion. It is too early for an accurate analysis of the hospital facilities within the Commonwealth, but it seems apparent that existing pediatric beds in many of the small community hospitals are not being economically utilized. There is a tendency for them to be filled at times, as during the tonsillectomy season, and to lie idle at other times, even while ambulances scream on occasion past their doors at considerable risk to both passengers and traffic, carrying patients to crowded pediatric centers in distant cities. This waste of facilities results from a lack both of trained pediatric personnel and of equipment. Given a local practitioner trained in pediatric care, however, and he will see to it that the equipment is eventually forthcoming and that the number of patients who have to be taken for a ride will reach an irreducible minimum.

Centralization has about reached its effective peak, and it is time to pay more attention to developing a self-contained community service. In this development the chief need is for pediatrically trained physicians in these communities. Time was when the specialist in the city counted as one of his activities the care of his consultation practice in the surrounding countryside. Then came the day of the screaming ambulance. We are now entering the more satisfactory era of the well equipped, well staffed community hospital where all but the most unusual cases can receive adequate care.

### MASSACHUSETTS MEDICAL SOCIETY COMMITTEE TO CONFER WITH GENERAL HAWLEY

The attention of Society members is called to the following contract recently approved by the Veterans Administration and the Committee to Confer with General Hawley of the Massachusetts Medical Society:

The Massachusetts Medical Society and the Veterans Administration, for the purpose of establishing and maintaining a close working relationship in order to establish a well integrated service for providing medical care and treatment for veterans of the State of Massachusetts beyond those services available to the Veterans Administration in existing Veterans Administration facilities and installations, do hereby mutually agree as follows:

- (1) The Massachusetts Medical Society will request all of its members to participate in a state-wide program whereby physicians in private practice in the State of Massachusetts will render medical services (examinations, treatments and counsel) in such cases as may be specifically authorized by the Veterans Administration
- (2) The Massachusetts Medical Society will submit to the Veterans Administration a list of its members who desire to provide service for eligible veterans in the home communities of such veterans. This list may be augmented from time to time as additional physicians may indicate a desire to participate in the program. The physicians so listed will be fee-basis physicians of the Veterans Administration. By notice in writing a physician may at any time request that his name be removed from the list of fee-basis physicians
- (3) The Massachusetts Medical Society will assist the Veterans Administration in establishing for examinations and treatment, a list of competent specialists who meet the qualifications of specialists of the Veterans Administration
- (4) Lists of physicians submitted by the Massachusetts Medical Society will be broken down by counties or districts in order that the veterans for whom services are authorized may select a physician practicing in his home community. The choice of the physician by the veteran provided for herein, is not applicable to examinations for pension or compensation rating purposes. Such examinations may be performed only by a physician specifically designated for that purpose by the Veterans Administration
- (5) Fees for medical services in authorized cases shall be paid by the Veterans Administration to the physician rendering the service in accordance with the fee schedule hereto attached which is made a part of this agreement. The Massachusetts Medical Society warrants that the rates set forth herein are not in excess of the rate of fees charged other persons who are not Veterans Administration beneficiaries for the same or comparable services. It is mutually understood that the fees stated in the fee schedule represent the maximum amount that may be charged, and do not represent the amount to be paid in every case. The Veterans Administration will advise each physician of this provision and will require each physician to certify in submitting his statement of account that the fees charged are not in excess of the fees charged by him for comparable service rendered nonveterans. It is understood that unusually involved cases and services not scheduled will be subject to review and recommendation by the Massachusetts Medical Society to the Veterans Administration for determination of the appropriate fee.
- (6) The Veterans Administration will handle administrative and clerical details in connection with the authorization of examinations or treatment and the maintenance of records and will arrange for transportation of the veteran if necessary
- (7) When authorizing treatment, the Veterans Administration will furnish to the veteran proof of such authorization and a list of fee basis physicians in the county or district in which the veteran is located in order that he may select his own physician for the services authorized
- (8) The Veterans Administration will review reports of examinations and services to determine their adequacy. No fees will be paid by the Veterans Administration for reports which are not acceptable to the Veterans Administration or for services rendered in unauthorized cases.
- (9) The Massachusetts Medical Society will establish one or more boards of review composed of physicians. It shall be the duty of such board to review reports which are deemed by the Veterans Administration to be inadequate or which do not

meet the requirements of the Veterans Administration to recommend at its discretion the disqualification of any physician for further work with the Veterans Administration whose work is found by the board to be incomplete or unsatisfactory, to advise and assist the Veterans Administration on other matters within the scope of this program

- (10) It is agreed that services furnished under the agreement will be performed by licensed physicians. It is further agreed that physicians rendering services hereunder will be citizens of the United States who are doctors of medicine duly licensed to practice medicine and surgery in the State of Massachusetts
- (11) This agreement shall be effective from July 1, 1947 to July 1, 1948, and may be terminated by either party by giving thirty days written notice to that effect.
- (12) This agreement, if mutually satisfactory, may be renewed indefinitely for a period of one year each, upon notice in writing to the Massachusetts Medical Society at least sixty days prior to the expiration of each period of one year and written statement from the Massachusetts Medical Society within thirty days after such notification agreeing to the renewal.
- (13) No member of or delegate to Congress or resident commissioner shall be admitted to any share or part of this agreement or to any benefit that may arise therefrom unless it be made with a corporation for its general benefit.
- (14) The Massachusetts Medical Society agrees that in performing this agreement it will not discriminate against any employee or applicant for employment because of race, creed, color or national origin
- (15) The Massachusetts Medical Society does not propose to make any charge for any service rendered to the Veterans Administration under this agreement.

In his letter accompanying this contract, General Hawley advised that it had been found necessary to adopt a policy that no physician will be permitted to accept fee-basis cases for the Veterans Administration in excess of \$6000 in any one year without the prior approval of the Administration and that all branch medical directors had been instructed to enforce this policy and to advise all participating physicians that it is in effect.

He also called attention to the fact that in the paragraph providing that physicians shall be licensed a provision had been added that they must be citizens of the United States, as required by law.

He concluded with the statement that it was understood that the Massachusetts Medical Society had agreed to accept the new *Veterans Administration Fee Schedule* (Form 10-2535a), which was attached to and made a part of the agreement.

HUMPHREY L. MCCARTHY, *Chairman*

## SECRETARY'S OFFICE

Attention should be called to the fact that a Boston physician's secretary was recently persuaded to advance money to a person posing as Dr. Stanley Rathbun, a cardiologist from New York City, who was temporarily out of funds after a professional trip to Boston. He claimed to be a friend of the secretary's employer, knowing him through

the New York Polyclinic and the Academy of Medicine. He is about five feet, eight inches tall and fifty-five to sixty years old and has dark hair that is on the thinnish side, at the time he was well dressed in a dark-brown suit. He is well versed in medical terminology, especially concerning the heart, and is quite garrulous. It was subsequently learned that he had given a false New York address and was not connected with the Polyclinic.

JOSEPH GARLAND

#### DEATHS

**GRADY** — Henry M. Grady, M.D., of Dedham, died on July 30. He was in his seventy-third year.

Dr. Grady received his degree from Harvard Medical School in 1905. He was town physician in Dedham for thirty-two years until his retirement two years ago.

Three brothers and two sisters survive.

**HARRIS** — Charles E. Harris, M.D., of Hyannis, died on May 21. He was in his seventy-ninth year.

Dr. Harris received his degree from Baltimore Medical College in 1897. He was a former president of the Barnstable District Medical Society.

His widow, two daughters and a son survive.

**HENNESSEY** — Thomas F. Hennessey, M.D., of Swampscott, died on July 21. He was in his sixty-first year.

Dr. Hennessey received his degree from Tufts College Medical School in 1911. He was a member of the American Congress of Physiotherapy and a fellow of the American Medical Association.

His widow survives.

#### MEDICOLEGAL ABSTRACT

**Liability for Malpractice. Refusal to attend patient without sufficient information regarding symptoms.** A recent New Hampshire decision illustrates the danger of a physician relying on a statement of a patient's symptoms given him over the telephone without eliciting adequate information. The patient, a pregnant woman, had begun to flow toward the end of the fifth month of pregnancy and remained in bed for the following two days on the doctor's advice. On the fourth day the flowing had practically stopped. On the sixth day she awoke in pain. According to her evidence her husband called the physician twice during the morning, saying that she complained of severe pains and asking him to come over. This was apparently the first child for the couple, and neither of them recognized the pains as labor pains, which, in fact, they were, so that, of course, the husband did not tell the physician that his wife was having labor pains. After a third call from the husband, in which he reported that a premature birth, referred to in the opinion as "miscarriage," had taken place on the toilet, the doctor came.

The court held that it was for the jury to determine "whether the defendant gave proper consideration to what he knew about the plaintiff's case, whether he used due care in eliciting information from the husband at the times of the first two telephone calls, if they occurred, that would have informed him that the plaintiff was in labor and

whether he was negligent in not attending the plaintiff before she had gone to the toilet and the birth had taken place." The court did not say that the failure of a physician to attend his patient simply because he is asked to is negligent, but recognized that under some circumstances a doctor may be under a duty to ask enough questions to obtain the information required to determine whether or not he is needed.

The court held that the plaintiff was not entitled to any damages for the mere fact of the premature birth, which would have occurred anyway, or for the physical and mental suffering that she would have endured under the usual circumstances that would have accompanied the premature birth, but that she was entitled to damages for the suffering that would have been avoided if the physician had been in attendance. The court pointed out that the child would have been born in bed, and that narcotics and other medicines could have been prescribed to relieve the pain and other care given. The court apparently considered that if the patient was improperly deprived of the doctor's attendance, she was entitled to damages for the loss of the "comfort" of his "assuring presence" and that she was entitled to damages for her "injured feelings attending the happening of the birth in the way it did" (*Mehigan v. S—*, N.H. 51 A [2d] 632).

#### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

##### ELECTIVE TONSILLECTOMIES DURING THE POLIOMYELITIS SEASON

Attention was recently called in this column to the advisability of scheduling as many elective tonsillectomies before August 1 as possible, it being noted that after that date further operations would depend on the prevalence of poliomyelitis in the vicinity.

Late in July cases of poliomyelitis began to appear with some regularity in the Metropolitan Area, which marked a warning that the seasonal upswing was imminent. It therefore appears wise to cease scheduling elective tonsillectomies in this area. On the other hand, only three cases of the disease were reported during June and July west of the Metropolitan Area. This indicates that it is safe to continue operations in the western part of the Commonwealth pending an increase in that area. During the same period no case of the disease occurred in the Merrimack Valley, and the same conclusion is warranted.

By the time this note appears in print the situation may have changed considerably in one or both of these areas. All local boards of health and various other agencies receive weekly information regarding the prevalence of poliomyelitis, and the continuance of elective tonsillectomies should be governed accordingly.

# COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JUNE, 1947

DISEASE	RÉSUMÉ		
	JUNE 1947	JUNE 1946	SEVEN YEAR MEDIAN
Chancroid	1	1	1*
Chicken pox	182	1400	1267
Diphtheria	3	21	11
Dog bite	1472	1318	1266
Dysentery bacillary	11	2	2
German measles	90	57	535
Gonorrhea	516	326	355
Granuloma inguinale	0	1	0*
Lymphogranuloma venereum	0	1	0*
Malaria	8	58	12
Measles	1290	7876	3923
Meningitis, meningococcal	3	4	16
Meningitis, Pfeiffer bacillus	5	2	2
Meningitis pneumococcal	3	2	4†
Meningitis, staphylococcal	0	0	1†
Meningitis, streptococcal	0	1	0†
Meningitis other forms	1	0	3†
Meningitis, undetermined	1	6	0†
Mumps	888	518	766
Pneumonia, lobar	99	63	207
Poliomyelitis	2	0	1
Salmonellosis	27	38	8
Scarlet fever	182	423	791
Syphilis	243	371	191
Tuberculosis, pulmonary	268	186	64
Tuberculosis, other forms	6	11	22
Typhoid fever	0	3	4
Undulant fever	16	3	5
Whooping cough	507	51	579

\*Three-year median

†Five-year median

## COMMENT

The diseases above the seven year median are chicken pox diphtheria dog bite, bacillary dysentery Pfeiffer bacillus meningitis pulmonary tuberculosis and tuberculosis, other forms and undulant fever.

The diseases below the seven year median are gonorrhea malaria, meningococcal meningitis mumps salmonellosis syphilis and whooping cough. Considerably below the seven year median are German measles measles lobar pneumonia, scarlet fever and typhoid fever.

Only two cases of poliomyelitis were reported.

Diphtheria did not show such a marked seasonal decline as would be desired. The number of cases reported did not decrease appreciably from the levels of the two preceding months.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from: Avon 1 Barnstable, 1 Beverly, 1 Billerica 1 Boston, 9 Chelsea 6, Lynn 1 Walpole, 1; Revere 11, Somerville 3 Waltham 1 Water town 1 total 37.

Dysentery amebic, was reported from Fall River 1 total 1.

Dysentery, bacillary, was reported from Marblehead 1 Worcester (State Hospital), 10 total 11.

Lymphocytic choriomeningitis was reported from Cambridge, 1, total, 1.

Malaria was reported from Boston 3 Lawrence 1 Malden 1 Monson 1 Winthrop 1 Worcester 1 total 8.

Meningitis meningococcal, was reported from Boston, 1 Oxford, 1; Quincy 1 total, 3.

Meningitis, Pfeiffer bacillus was reported from Brockton, 2 Concord, 1 Oxford 1 total 4.

Meningitis pneumococcal, was reported from Framingham 1; Lexington 1 Watertown, 1 total 3.

Meningitis, other forms was reported from Boston 2 total 2.

Meningitis undetermined, was reported from Malden 1 total 1.

Poliomyelitis was reported from Boylston 1 Springfield 1, total 2.

Salmonellosis was reported from Boston, 3 Lawrence, 1 Lynn 1 Newton, 1 Worcester 1; total, 7.

Septic sore throat was reported from Boston 4 Easthampton 1 Greenfield 1 Merrimac 1 total 7.

Tetanus was reported from Boston 1, Springfield, 1 total, 2.

Trichinosis was reported from Boston 1 Waltham 1 total, 2.

Undulant fever was reported from Brookline 1 Lancaster, 1 Milford 1 Worcester 13 total, 16.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*The Complete Pediatrician. Practical, diagnostic, therapeutic and preventive pediatrics.* By Wilburt C. Davison, D.Sc. M.D. professor of pediatrics, Duke University School of Medicine, and pediatrician Duke Hospital. Fifth edition. 8° cloth 354 pp. Durham North Carolina: Duke University Press, 1946. \$4.00.

This unique manual has proved popular and useful as a ready reference source for all physicians and students called on to care for sick and healthy children. The whole field of pediatrics is covered in two hundred and fifty six topics of varying length. The material is arranged in thirteen chapters according to diseases of the body systems, to which are added laboratory procedures nutrition and feeding general and physical therapy and nursing growth and development and drugs and prescriptions. An ingenious system of cross reference from one topic to another makes readily available all information on a given subject contained in the volume. A comprehensive index completes the book. Emphasis is placed on diagnosis and treatment. In the laboratory section two hundred and two of the best practical methods are described. This manual contains a wealth of condensed information and should prove useful to all physicians.

*The Problem of Fertility. Proceedings of the Conference on Fertility held under the auspices of the National Committee on Maternal Health.* Edited by Karl T. Engle. 8° cloth 234 pp., with 28 illustrations. Princeton Princeton University Press 1946. \$3.75.

Nineteen leaders in research in the field of fertility read papers at the Conference on Fertility held in February 1946, at Princeton University, and these articles are brought together in this volume. The articles summarize the research done on domesticated animals and on man. The participants were animal husbandrymen and clinical researchers who met probably for the first time in a joint conference, to discuss a topic of mutual interest.

The points covered in the discussions include the relation of fertility to the time of ovulation the effect of the condition of the cervical mucus and the viability motility and fertilizing capacity of spermatozoa. Consideration was given to human fertility as well as to that of laboratory and domesticated animals. Pertinent bibliographies are attached to the articles. The volume is well published. It is recommended for all medical libraries as a reference book.

*Preoperative and Postoperative Treatment.* Edited by Lieutenant Colonel Robert L. Mason, M.C., A.U.S., Cushing General Hospital and Harold L. Zintel M.D., Harrison Department of Surgical Research University of Pennsylvania School of Medicine and assistant surgeon, Hospital of the University of Pennsylvania. Second edition. 8° cloth 584 pp., with 157 illustrations. Philadelphia W B Saunders Company 1946. \$7.00.

This composite work of twenty collaborators has been revised to include the important advances in surgery occurring since the publication of the first edition in 1937. The type has been completely reset and nearly every chapter has been rewritten. The following new material has been added: physical medicine in surgical practice preoperative and postoperative care in gynecology and surgery of the stomach and duodenum intestinal obstruction nutrition in surgery, surgical risk in pregnancy thrombophlebitis vitamin K therapy and emergency care in cranial injuries. A selective bibliography is appended to each chapter and the text is printed with a good type on heavy coated paper, resulting in a volume that is much too heavy for its size. The book is in all medical libraries and in the libraries of



*Henry Sewall Physiologist and physician* By Gerald B Webb and Desmond Powell 8°, cloth, 191 pp., with 10 plates Baltimore Johns Hopkins Press, 1946 \$2.75

This is a well written biography of an eminent American physician and scientist. Educated at Wesleyan and Johns Hopkins universities, he studied abroad and on his return to the United States became an assistant in physiology at Johns Hopkins University School of Medicine and, in 1882, professor of physiology at the University of Michigan. Afflicted with tuberculosis, Sewall went to Colorado in 1888 and, after doing some work in medicine, was given an M.D. degree by the University of Denver. In 1889, because of his disease, he became a resident physician at the Trudeau Sanatorium at Saranac Lake, remained there a short time, and then began to practice in the near-by town of Lake Placid. In 1890 he went to Denver to remain permanently, practicing medicine and serving on the Board of Health and on the faculty of the University of Denver as professor of physiology, he was also professor of medicine at the University of Colorado Medical School. He became eminent as a physician, specializing in tuberculosis, and was elected a member of the Association of American Physicians in 1900, the highest medical honor of its time. He was elected president in 1916. He died at his home in Denver on July 8, 1936. A bibliography of the writings of Dr. Sewall and an index conclude the volume. This delightful biography is well published and should be in all medical libraries and medical-history collections.

*Clinical Hematology* By Maxwell M. Wintrobe, M.D., Ph.D., professor of medicine, University of Utah School of Medicine. Second edition, thoroughly revised. 8°, cloth, 862 pp., with 197 illustrations and 14 plates, 10 in color. Philadelphia: Lea and Febiger, 1946. \$11.00.

This standard textbook on its subject has been thoroughly revised and brought up to date. The book, which is well published, is recommended for all medical libraries and should prove useful to physicians interested in diseases of the blood.

*Yearbook of Psychoanalysis* Volume II, 8°, cloth, 280 pp. New York: International Universities Press, 1946. \$7.50.

The second volume of this annual contains fourteen articles by recognized authorities in the field of psychoanalysis reprinted from various publications of 1945, some of which are relatively inaccessible. The publication in one volume brings them together for ready reference. The yearbook is recommended for all medical and psychiatric libraries.

*X-Ray Diffraction Studies in Biology and Medicine* By Mona Spiegel-Adolf, M.D., professor of colloid chemistry and head, Department of Colloid Chemistry, Temple University School of Medicine, and George C. Henry, M.D., professor of medical physics, Temple University School of Medicine. 8°, cloth, 215 pp., with 87 illustrations. New York: Grune and Stratton, 1947. \$5.50.

Monographs on this difficult subject have been written for the physicist and chemist, but this is the first discussion in English for the biologist and research physician. Purely physical and mathematical discussions have been omitted wherever possible. The text comprises a survey of the literature of the subject combined with the studies of the authors carried on during the past ten years. The beginning chapters discuss the theory, apparatus and technique and interpretation of x-ray diffraction patterns. Special chapters are devoted to the biologic substances, including carbohydrates, amino acids, proteins, nucleic acids and nucleoproteins, lipids and steroids, and to muscle, nerves, bones, teeth and concretions. The chapter on the proteins is comparatively large, owing to the amount of work done in this field. To each chapter is appended a list of selected references. Author and subject indexes conclude the volume, which is well published in every way. The work should be in all medical reference collections and in all biologic laboratories.

*Physical Medicine in General Practice* Edited by Arthur L. Watkins, M.D., 8°, cloth, 341 pp., with 15 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$5.00.

This symposium by fourteen specialists, originally published in *Clinics*, is brought together for the benefit of practicing physicians. The fields of medicine, surgery and the various specialties in which physical therapy has proved of value are well covered. The articles on rehabilitation and employment, and on reconditioning in some Army hospitals are particularly timely. There are special articles on fever therapy and chemotherapy and on the use of cold in medicine and surgery. To each article is appended a list of references to recent literature. The articles are concise and well written. The volume is well published and should prove useful to the practicing physician.

## NOTICES

### MEDICOLEGAL CONFERENCE AND SEMINAR FOR PATHOLOGISTS, MEDICAL EXAMINERS AND CORONERS

Beginning on Monday, October 13, the departments of legal medicine of the medical schools of Harvard, Tufts and Boston University, in association with the Massachusetts Medico-Legal Society, will present at Harvard Medical School a six-day program of lectures, conferences and demonstrations having to do with the investigation of deaths in the interests of public safety. Attendance will be limited to twenty-five persons who have registered in advance. Further information may be obtained from the Department of Legal Medicine, 25 Shattuck Street, Boston.

### NORFOLK DISTRICT MEDICAL SOCIETY

The Norfolk District Medical Society will hold its 1947-1948 meetings at the Boston Medical Library, 8 Fenway, Boston. The meetings will start at 8 p.m. Detailed notices of all meetings will appear at later dates.

Tuesday	September 23	Boston University Night
Tuesday	October 28	Lahey Clinic Night
Tuesday	November 25	Tufts Night
Tuesday	January 27	Round-Table Discussion Bleeding from the Alimentary Tract
Tuesday	February 24	Obstetric and Gynecologic Night
Tuesday	March 23	Harvard Night

Collations will be served

### AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

At the annual meeting of the American Board of Obstetrics and Gynecology, held in Pittsburgh from June 1 to 7, a number of changes in regulations and requirements were put into effect. Among these is the new ruling that the Board does not subscribe to any hospital or medical school rule that certification is to be required for medical appointments in rank lower than chief or senior staff of hospitals or associate professorship in schools of medicine, for the obvious reason that such appointments constitute desirable specialist training. At this meeting the Board also ruled that credit for graduate courses in the basic sciences that involve laboratory and didactic teaching rather than clinical experience or opportunities will be given credit for the time spent up to a maximum period of not more than six months, regardless of the duration of the course.

The next written examination (Part I) for all candidates will be held in various cities of the United States and Canada on Friday, February 6, 1948, at 2:00 p.m. Applications are now being received for these examinations, and the closing date for the applications is November 1. Further information and application blanks may be obtained from Paul Titus, M.D., Secretary, 1015 Highland Building, Pittsburgh 6.

(Notices continued on page xix)

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## SPECIFIC READING DISABILITY\*

### A Familial Syndrome Associated with Ambidexterity and Speech Defects and a Frequent Cause of Problem Behavior

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CHILDREN who have not learned to read or to read fluently and with understanding are almost disgracefully numerous in our schools. Educational literature gives no clear picture of why this is so. The list of reasons advanced for their failure is a long one and includes such items as low intelligence, physical illness, malnutrition, visual and auditory defects, immaturity, lack of interest, emotional blocking and poor teaching. The viewpoint of the majority of teachers and child psychologists is clearly expressed by Witty and Kopel,<sup>1</sup> who, after full discussion of the various causes, state emphatically that there is no single specific cause, but that causation must be sought in a composite of related conditions.

On the other hand, physicians<sup>2-9</sup> and a few educators<sup>10-12</sup> maintain that buried in the amorphous mass of children who fail for a multiplicity of reasons—physical, mental, psychologic and social—is a hard kernel of children of a distinctive type. They are predominantly boys whose weakness in the use of language is definitely out of keeping with their skills in other directions, particularly in arithmetic. Many are late in learning to talk and, when they do talk, are likely to lisp or stutter. They are apt to be more or less ambidextrous. Their family trees, when accurate histories are obtainable, are found to contain a large number of similar persons. When such children are studied, it becomes clear that in this restricted group there does exist a single factor that plays a large part in their reading difficulties. This factor is believed to be an inherited sex-associated weakness of the language function combined with a tendency to ambidexterity. The name given to this syndrome is "specific language disability." When the difficulty is chiefly with reading,

it is called "specific reading disability" or "strophosymbolia" (Orton<sup>3</sup>).

This disagreement between educators and psychologists on the one hand and physicians on the other would be of no practical import were it not for the fact that most schools fail to separate children with specific reading disability from other poor readers. The result is often tragic failure for the children with the specific disability.

This is a report on 23 carefully studied children with specific reading disability. They were selected from a larger group of 33 who were examined because of school failure or problem behavior. For the 10 children eliminated from the group the diagnoses were encephalitis, low I.Q., hypothyroidism, poor teaching and poor discipline.

#### MATERIAL AND METHODS

The children in this group were followed for an average of eight years—some for as few as two years, and others for as many as sixteen. All were private patients coming from twenty-one families. The status of all but one of the homes was known. Two could be classed as high average, and the others as definitely superior. The occupations of the fathers were as follows: business, 9; university professor, 7 (4 of these were physicians); professional, 3; gentleman farmer, 1; and clerical, 1.

Seventeen children attended private schools of excellent reputation. Six had started in public school in good residential districts, but 5 of them, when their difficulties were recognized, changed permanently or temporarily to selected private schools where individual tutoring could be supplied.

These 23 children were in normal physical condition except for one with hemiplegia. The vision of 20 either was normal or had been corrected by glasses. Three had defective vision in one eye only; their hearing was normal. Psychometric tests

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(Stanford-Binet) on 17 gave results ranging from an IQ of 85 to one of 136. The true levels were probably a few points higher, since it is generally admitted that children with specific reading disability are handicapped in certain of the tests. There were only 5 with levels below 100, and their performance was judged according to their mental ages. Because their parents opposed it, 6 were not tested, but these children were well known by the examiner, who considered their intelligence to be at least normal.

The group were given standardized scholastic achievement tests that graded skill in arithmetic,

defects or difficulty in reading and spelling. Here the examiner's knowledge of the family was a great help in uncovering otherwise forgotten details. A note was also made of any unusual behavior on the part of the children.

Young infants are equally clumsy with both hands and should therefore be described as ambilateral instead of ambidextrous. By the end of the second year, one hand has usually been chosen more and more for skilled activities,\* and habitual use strengthens and confirms the selection. The majority believe that handedness is determined by Mendelian inheritance,<sup>3, 4, 13</sup> although Blau<sup>14</sup> argues

TABLE 1 Pertinent Data in 23 Cases of Specific Reading Disability

CASE No	SEX	AGE AT FIRST EXAMINATION	PRESENT AGE	BEHAVIOR PROBLEM	SCHOOL FAILURE	INTELLIGENCE QUOTIENT	FAMILY HISTORY OF DISABILITY	SPEECH DELAY
1	M	7	25	Yes	Yes	96	Yes	—
2	M	6	14	—	Yes	Not tested	Yes	Yes
3	M	11	13	—	Yes	117	Yes	—
4	M	11	16	Yes	—	136	Yes	—
5	M	7	15	Yes	Yes	Not tested	Yes	—
6	M	9	15	—	Yes	107	No	Yes
7	M	7	12	—	Yes	Not tested	Yes	—
8	M	6	14	—	Yes	98	Yes	—
9	M	12	28	—	Yes	120	Yes	—
10	F	8	19	Yes	Yes	Not tested	Yes	—
11	M	10	19	Yes	Yes	121	No	—
12	M	11	22	Yes	Yes	102	No	—
13	M	6	15	—	Yes	117	No data	—
14	M	9	15	Yes	Yes	92	No data	—
15	M	9	18	—	Yes	96	Yes	Yes
16	M	9	16	—	Yes	Not tested	Yes	Yes
17	M	7	21	Yes	Yes	110	Yes	—
18	M	8	12	Yes	Yes	128	Yes	—
19	M	8	17	Yes	Yes	106	Yes	—
20	M	8	10	Yes	Yes	100	Yes	Yes
21	M	6	13	Yes	Yes	100	Yes	Yes
22	F	6	20	Yes	Yes	85	Yes	—
23	F	7	16	—	Yes	Not tested	Yes	—

\*Crossed laterality  
†Vision of other eye defective  
‡Patient had hemiplegia

silent reading, oral reading, reading speed and spelling. All made scores in arithmetic that corresponded approximately to the mental age. In their reading and spelling skills, however, they were from one to three or even four grades behind. They either were unable to read or read slowly and without much understanding. Frequently, they failed to recognize simple words and tended to confuse such letters as "b" and "d," and to reverse short words such as "on" for "no" and "was" for "saw" or syllables such as "astrep" for "repast." The handwritings were, in general, poor, and the spelling was worse. Because of this specific failure in reading, which was out of all proportion to their skill in other lines, these children were classed as cases of specific reading disability.

They were also tested to determine the leading hand and eye. Note was made of any defect in speech. The parents were questioned on previous defects in speech or delay in learning to talk, as well as on a family history of other members who were left-handed or ambidextrous or who had speech

that most people are right-handed because of social and cultural pressure and the minority left-handed because they were strongly negativistic in early childhood. According to the inheritance theory, since mankind is of mixed stock (heterozygous) so far as handedness is concerned, the offspring present a series of intergrades between a few strong dextrals at one end and few strong sinistrals at the other. Practically, however, the race is predominantly right-handed, and has been so since the Bronze Age,<sup>11</sup> although nobody knows why. It seems evident that the pressure of existence in this right-handed world shifts most of the intergrades toward the right.

Laterality tests are used to determine approximately where in this series of intergrades the subject should be placed — that is, whether his handedness is right, right with some left, left with some right or left. Questioning or observation while the subject is performing trained activities such as writing gives results heavily in favor of the right hand.

\*Cobb<sup>4</sup> and Blau<sup>14</sup> have presented studies on the relation between handedness and language.

A battery of tests completed while the subject is in ignorance of the examiner's purpose gives a truer picture and usually shows more evidence of partial ambidexterity. The amount of ambidexterity reported varies with the author's definition of the term and the technic used in testing. The consensus seems to be that at least 75 per cent of school children and adults are right-handed and 25 per cent either left-handed or partly ambidextrous.<sup>12-14</sup>

In these tests the children were asked to use a few simple tools, such as a hammer, screw driver and scissors, and to play a xylophone, throw a ball, swing a bat, wind a watch, wind up a ball of string,

## FINDINGS

Table 1 presents the sex, age and presenting complaints of these children, as well as their preferences of hand and eye, degrees of specific reading disability, I Q's, the presence of speech defects or of delay in learning to speak, the existence of similar conditions in the family history and, finally, the type, duration and result of treatment.

### Handedness

The hand originally preferred by one boy (Case 12) could not be determined because of hemiplegia. Of the remaining patients only 4 were right-handed,

TABLE 1 (Continued)

CASE No.	SPEECH DEFECT	HANDEDNESS	EYEDNESS	DEGREE OF DISABILITY	REMEDIAL TREATMENT		
					BY SCHOOL	BY APPROVED TUTOR	RESULT
1	Yes	Right with left	Right with left	Moderate	37	37	Poor
2	Yes	Right with left	Left with right*	Mild	50	—	Good
3	—	Right	Left*	Mild	10	—	Good
4	Yes	Right with left	Left†	Mild	No d. ta	—	Good
5	—	Right	Right	Moderate	20	—	Good
6	Yes	Left with right	Right*	Mild	20	—	Good
7	—	Right with left	Left with right*	Mild	20	—	Good
8	—	Left with right	Left with right	Moderate	25	—	Poor
9	Yes	Left with right	Left	Severe	15	—	Good
10	—	Right with left	Right	Mild	10	—	Good
11	—	Left with right	Left	Mild	10	0 ?	Good
12	—	†	Left†	Mild	20	0	Good
13	Yes	Left with right	Right*	Mild	—	0 ?	Poor
14	—	Right with left	Right	Mild	10	0	Good
15	Yes	Right with left	Right	Moderate	10	15	Poor
16	Yes	Right with left	Left*	Severe	10	10	Good
17	—	Left with right	Right	Severe	50	10	Improvement
18	—	Right with left	Right	Severe	10	10	Good
19	Yes	Right with left	Right	Severe	30	10	Good
20	Yes	Left with right	Right*	Severe	10	20	Improvement
21	Yes	Right with left	Right with left	Moderate	10	10	Good
22	—	Right with left	Right	Moderate	50	10	Improvement
23	—	Right	Right	Moderate	30	10	Good

\*Crossed laterality

†Vision of other eye defective

‡Patient had hemiplegia

play cards, pick up cards dropped on the floor and, finally, write their names and a short sentence. If the subject showed evidence of being partly ambidextrous, he was then asked to write with his non-preferred hand, and the two signatures were compared. The results were scored as right, right with some left, left with some right and left.

To determine eye preference a few equally simple tests were used, such as asking the subject what he saw through a kaleidoscope, the examiner meanwhile noting which eye was used, having him identify an object held in front of the examiner's face while he was looking through an open cone whose large end covered both eyes, having him look through a small hole, and finally, having him point at the examiner first with the forefinger of one hand, then with the forefinger of the other and lastly with a pencil held simultaneously in both hands. The only precaution needed was to be sure there was no serious visual defect in either eye. The results were scored with the use of the same scale as in the hand tests.

18 were more or less ambidextrous, and none were left-handed. Eleven of the ambidextrous were right-handed with some left-handed skills. They considered themselves, and on casual observation would be classed as, right-handed. Seven of the ambidextrous were left-handed with some right-handed skills and would similarly be classed as left-handed. Thus, although from questioning or simple observation, 15 of the 22 subjects, or two thirds, would be considered right-handed and 7, or one third, left-handed — a ratio that is approximately the same as that of the general population<sup>12-15</sup> — the truer proportion was only one fifth right-handed, with four fifths more or less ambidextrous and none purely left-handed.

This great preponderance of ambidexterity is in accordance with the reports of physicians<sup>2-9</sup> on handedness in cases of specific reading disability. It is in great contrast to the reports by psychologists and educators, most of whom found no more left-handedness and ambidexterity in poor than in good readers.<sup>1</sup> It is also in great contrast to the generally

accepted standards of handedness in the general population<sup>13-15</sup> Finally, it strongly supports the theory that lack of clear manual dominance is closely associated with specific reading disability

This discrepancy between the results obtained by psychologists and educators on the one hand and neurologists on the other — followers of different although somewhat related disciplines — can only be explained by the assumption that identical groups have not been studied or that different methods and standards are used in the tests Therefore, instead of disputing each others' findings and conclusions, both groups should try to define more accurately the group that they are testing and to describe more clearly just how the tests on laterality are conducted and recorded

### *Eyedness*

Three children had defective vision in the right eye \* Of the remainder 11 sighted with the right eye, and 4 with the left eye, and 5 were amblyopic — 2 with a preference for the right eye, and 3 for the left Seven showed "crossed laterality" in that the eye preferred for sighting was on the opposite side from the preferred hand One of these was right-handed and left-eyed The others were partly ambidextrous 3, preferring the right hand for most acts, sighted usually or entirely with the left eye, and 3, preferring the left hand, were right-eyed

The significance of these figures on eyedness is not clear There is certainly no such predominance of amblyopia in these children as there is of ambidexterity, and the number with crossed laterality is apparently no greater than that in normal children<sup>15</sup>

### *Family Histories*

In hospital clinics, and presumably in schools as well, it is difficult to obtain satisfactory family histories of delay in learning to talk, speech defects, ambidexterity and reading disability The pediatrician in private practice has a far better opportunity to obtain them because he has been in the homes and is more or less acquainted with other members of the family

In this series of cases of specific reading disability, there was a history of left-handedness or ambidexterity or of one of the above-mentioned forms of language disability in 18 of the 21 families (85 per cent) in which the information was asked for and recorded This high incidence and particularly the study of some of the individual family trees afforded strong evidence that the trait resulting in these conditions is inherited

### *Effect on Behavior*

Frustration is now recognized as one of the underlying causes of problem behavior such as showing off, lying, stealing, arson or withdrawal from the

group into solitude, as well as of complaints of a more medical nature, such as enuresis, indigestion and obesity Certainly, these children were seriously frustrated by their school failure, and it is interesting that the records of only 10 make no mention of unusual behavior or illness

Five children were solitary and comparatively friendless, 2 were obese from simple overeating 2 lied habitually, 2 stole habitually, 2 were known to masturbate (1 of these had sexual relations with his sister and also undressed before a mixed group of children), 1 terrified his parents by threatening to run away, 1 set the barn on fire, 2 had indefinite illnesses associated with school tests, and 1 with an I Q of 120, who managed to control himself at the time, has since admitted that at the age of twelve and a half he felt sure that he was a "moron" One of the obese children and 1 sex offender came from broken homes — a fact that was undoubtedly partly responsible for their behavior

### TREATMENT†

The diagnosis of specific reading disability means that the patient's poor schoolwork and problem behavior are due to the way he is made and to the manner in which his brain and nervous system function, not to laziness, stupidity, lack of interest, poor concentration or any physical ailment or abnormality Quite literally, he is unable to learn reading the way it has been presented to him but can learn although slowly, if a different approach is used

The basic difficulty with these children seems to be that for part of the time, but only for part of the time, they try to read from right to left A word or a letter read correctly on one line may be read backward in whole or in part on the next line, and the resulting errors make utter nonsense

Therefore, the basic aim in teaching reading and writing to these children is to establish firmly in their minds and fingers the correct left-to-right sequence and the shapes, names and sounds of the letters Because their visual images are uncertain they are helped (as most persons are in memorizing) by kinesthetic reinforcement — that is, by looking at the letter, saying it and writing it simultaneously They are gradually taught to blend the sounds into short words and then into longer words Eventually, as they master reading, they learn to recognize whole words just as those who were taught from the first by the whole-word method do Even after they are reading more or less successfully, the letter drills must be continued to prevent a setback Throughout, the emphasis is on accuracy and understanding rather than on speed, which may or may not come later according to the interests, aptitudes and opportunities of the children Unless there are other factors in the situation, the short attention span, the emotional blocking and the behavior problems tend to disappear as the child

\*It should be noted that specific reading disability may occur in children with monocular vision

†Detailed accounts of treatment have been presented by Orton<sup>1</sup> and by Gillingham and Stillman<sup>16</sup>

gains confidence in his ability to learn by this method

The actual treatment is best conducted by a skillful teacher who has enough understanding of child psychology and of the working of the nervous system to know what she is trying to do. The best results are obtained from individual tutoring for a half to one hour, five days a week, for periods of one, two or three years. The length and intensity of the tutoring depends on the intelligence of the child, the severity of his disability and his age. Younger children, other things being equal, respond far more quickly than older ones in whom years of failure have produced well justified discouragement and emotional tensions.

### *Practical Difficulties*

Once the diagnosis has been made and the situation explained to the parents, the physician would like to hand the treatment of his patient over to the school. Unfortunately, this is seldom the best course, and then only for mild cases attending schools with good remedial teachers. Although most schools recognize reading disability and many schools have remedial reading classes, few distinguish cases of specific reading disability from their other poor readers, and fewer still are prepared to supply the intensive individual and long-continued tutoring required for the best results. The classes in remedial reading are overcrowded, and the teachers usually overworked and under constant pressure to return their pupils to the regular classes as soon as possible. The result is that pupils with a mild degree of disability — or even a moderate degree, if their intelligence is high — may learn to read after a fashion, but not well enough to do good work in the upper grades. The severer cases and patients of only average intelligence, if in public schools, are apt to end up in special classes, where they certainly do not belong, and if in private schools, to transfer from school to school in constant hope that a miracle will occur.

Therefore, it is usually necessary to advise individual tutoring by a specially trained teacher. This tutoring is best done at the school during the periods when the rest of the class are working on English so that it will not interfere with the pupil's other studies. Also, since it is not a punishment, it should never be allowed to interfere with the pupil's time off for play. Arranging for this remedial tutoring requires the consent of the school head. Although some headmasters are co-operative, others are not, perhaps through no fault of their own, and it may become necessary to transfer a pupil to some school where the tutoring can be managed.

### *Results*

The patients varied so in their aptitudes, interests and intelligence that it was difficult to establish satisfactory standards for the degree of specific reading disability from which each one suffered and equally difficult to assess the degree of improvement

shown by each as the result of treatment. In general, a child who was retarded one year in reading was classed as a mild case, one two years as a moderate case, and one three or more years as a severe case. It soon became evident, however, that a second grader one year behind in reading was much worse off than a fifth grader one year behind, and consequently the examiner's personal impression and knowledge of the patients were taken into consideration in the classification of each case as mild, moderate or severe. Even so, this grading must be regarded as relative and not absolute.

All the children eventually learned to read — even the two who had little or no real remedial tutoring. For those who are now doing satisfactory school or college work without assistance or have graduated, the result is classed as "good." For those whose disability has seriously affected their education and future livelihood, the result is classed as "poor." Those between the two extremes are classed as "improved."

### *Good Results*

The IQ's of the 16 children who had good results were normal or above, the average for the 10 children who were given psychometric tests being 113.

*Remedial work by the school only.* All the schools involved had good teachers of remedial reading. Six of the 8 children whom they handled successfully without outside help had mild cases. The duration of the remedial training was one to five years.

In Case 5, in which the disability was moderate, the patient had two years of remedial training and then went to boarding school, where he is doing fairly well.

In Case 9, in which the disability was severe, the patient was bright enough to conceal his disability until he was twelve, and then on a change of schools failed completely. After a year and a half of remedial training at another school with a good remedial teacher, he did well at boarding school but was able to graduate from college only by avoiding reading courses.

These 8 children would surely have made faster progress in learning to read and thereby have avoided a considerable amount of discouragement and strain had they received skilled individual tutoring as soon as their disability was apparent. Such tutoring was urged for most of them but was refused by the parents largely because the school considered it unnecessary.

*Remedial work partly by the school and partly by an approved tutor.* In this group were 3 mild cases, 2 moderate, and 3 severe. The patients attended schools with good remedial teachers.

The patient in Case 11, whose disability was mild, was doing poorly in a school where he had had no remedial training. He was tutored individually for one summer only and then transferred

to a school whose remedial teacher continued to work with him for three years. He is now doing well at a college preparatory school.

In Case 12, with a mild disability, the patient needed two years of remedial work by the school and two more of individual tutoring before he responded. The slow progress was largely due to the mental and emotional depression associated with his hemiplegia.

In Case 12, in which the disability was mild, the patient failed to learn to read in the early grades and became a behavior problem. He was transferred to another school and given a year of individual tutoring under supervision and another by the school's remedial-reading teacher. At the end of that year he was reading up to his grade level and had become president of his class. His parents then returned him to his original school.

The patient in Case 21, whose disability was moderate, failed to learn any reading in the first half of the first grade and became a serious behavior problem. At the age of six and a half, his parents sent him to a boarding school, where his disability was not recognized until he was tested at the end of his third year. During the next year, the school's remedial teacher worked with him without any improvement. He was then put under an approved tutor in another boarding school with great improvement, and during the next year was taught by the school's remedial teacher, by the end of which time his reading was at his grade level and his behavior much better.

In Case 23, with a moderate disability, the school worked with the patient for three years before they asked for help. She was then given a year of individual tutoring, after which there was no further difficulty.

In Case 16, in which the disability was severe, the patient improved so rapidly after a year of individual tutoring that he needed only one more year by the school. His IQ was probably well above the average.

The patient in Case 18, whose disability was severe, needed two years of individual tutoring and then another after the lapse of one year.

In Case 19, a severe reading disability was recognized early. The school assured the parents that the remedial reading teacher could handle him successfully. He continued to do poorly, and on a teacher's advice was fitted with aniseikonic lenses without benefit. Finally, at ten and a half years, his failure was so obvious and he was so unhappy that he was tested thoroughly and was found to have a severe disability. His arithmetic score was also low, apparently because of his general discouragement. A year of individual tutoring produced great improvement. He then moved away for several years. On his return, he was given a little more individual tutoring and is now, at the age of seventeen, doing fairly well at a small boarding school.

### *Improvement*

One patient is still under treatment, 1 has a low IQ, and 1 received insufficient individual tutoring in view of the severity of his disability.

*Remedial work partly by the school and partly by an approved tutor.* The patient in Case 22, with a moderate disability, failed to learn to read in one school and was shifted to another, where there was a good remedial-reading teacher. After four years there, her work was still so poor and she was so unhappy that she was tested for the first time. A year of individual tutoring followed by more remedial work in another and smaller school helped immensely. She is still not a good reader, but her present difficulties are due more to the discrepancy between her IQ and those of her associates than to her poor reading. This result is classed as "improvement" rather than "good" because the inadequate handling of her disability is partly responsible for her present unhappiness.

In Case 17, in which the disability was severe, the patient had four years of remedial work in a selected school, and then one year of individual tutoring followed by another year's work by the school. At the age of twenty-one he is in college receiving honor marks in science and passing in English, but failing in the required foreign language.

In Case 20 the disability was severe, the patient was late in talking, had a speech defect and failed to learn to read in the first grade. He is in his third year of individual tutoring, and both his reading and his speech have improved rapidly under phonetic training. This result is classed as "improvement" instead of "good" because the reading is still below grade.

### *Poor Results*

*Remedial work by the school only.* In Case 1, with a moderate disability, a stuttering, partly ambidextrous, clumsy\* boy had a poor start with several changes of school and several years of teaching at home. His stuttering became worse, and finally, at the age of fifteen, he was tested and found to be two years behind in reading and four in spelling. Skilled individual tutoring was advised and refused. The next winter the patient broke his right arm, and while he had to use his left, both his stuttering and his school marks improved. Nevertheless, he refused to continue left-handed writing. He later went to a tutoring school, where he failed completely, and then to a small country boarding school, where he was much happier. He was in the Army for two and a half years. At the age of twenty-three years, the patient is teaching farming at the same small boarding school and is said to stutter only under great stress.

The patient in Case 8, whose disability was moderate, had two and a half years of remedial training in the first, second and third grades before

\*Apraxia is often part of the picture.

changing schools. He has continued to have trouble with reading and is now failing in a preparatory school.

*Remedial work partly by the school and partly by an approved tutor.* In Case 13, in which the disability was mild, the patient attended a school without good facilities for remedial reading. He has had only three months of approved individual tutoring. He has also been to a remedial-reading clinic for a few summers, but has received no consistent training through the school years. At the age of fifteen he is failing in a preparatory school. His reading comprehension is above that of his grade, but his reading speed is too slow for him to complete his assignments.

In Case 15 the disability was moderate. The patient failed to learn to read in the early grades. He then transferred to another school and received a year and a half of individual tutoring followed by another in the school's remedial-reading class. In view of his comparatively low I.Q., this was not enough. Nevertheless, instead of continuing the tutoring, his parents chose to make several successive changes of school. At the age of eighteen he is doing poorly and does not expect to try for college.

### DISCUSSION

These case histories were obtained from a carefully studied series of private patients, and what they lack in volume they more than make up in accuracy. They point out the difference between the term "reading disability," as used by most educators and psychologists,<sup>1</sup> and the more restricted diagnosis of specific reading disability. They make clear that the latter is a definite entity, occurring in children of all grades of intelligence, although work with those who are below the normal range is scarcely worth while. The histories confirm the opinion that patients can be discovered by means of scholastic achievement and psychometric tests, and that the diagnosis is strengthened by the finding of delayed or defective speech and ambidexterity in the child and in the family tree.

These cases also show that selected schools with good remedial teachers can obtain good results with mild cases of disability with a normal or better I.Q. (Cases 2-4, 6, 7 and 10), fair results in moderate cases with a normal I.Q. (Case 5) and even a good result in a severe case (Case 9), with a high I.Q. Ten cases illustrate the benefit of skilled individual tutoring (Cases 11, 12, 14, 16, 18, 19, 20, 21, 22 and 23), 2 the folly of frequent changes of school and methods (Cases 1 and 15), and 3 the difficulties that patients of good intelligence may have because of insufficient skilled individual tutoring (Cases 8, 13 and 17).

### SUMMARY AND CONCLUSIONS

Specific reading disability is a definite entity usually associated with ambidexterity and speech defects both in the patient and in the family tree.

Ambidexterity, left-handedness and speech defects are not causes of specific reading disability. They are merely frequently associated findings and as such are to be regarded as part of the same picture.

Crossed laterality and amphiccularity seem to occur approximately as often in normal children as in children with specific reading disability. They are, therefore, probably neither causes of the disability nor frequently associated findings.

Specific reading disability may occur in children of any degree of intelligence, but intensive treatment is hardly worth while in those who are below the normal range. Unrecognized or inadequately treated, it frequently results in frustration, discouragement and problem behavior. When properly treated, patients with normal to superior intelligence are able to do well in school and college.

Mild cases can be handled successfully by some schools, although they respond more quickly and with less discouragement and problem behavior to skilled individual tutoring. Moderately severe and severe cases need intensive individual tutoring for several years. The older patients, especially, need an interested and understanding physician or psychiatrist to supervise the course of treatment and to encourage them and their parents.

Frequent changes of school or of methods of treatment are of no benefit.

Children who do not learn to read in the first grade should be studied carefully, and if they prove to have specific reading disability, they should be taught to read, write and spell by phonetic and kinesthetic methods.

General practitioners and pediatricians should know enough about the subject to make a provisional diagnosis in cases of specific reading disability that may be brought to them for school failure or problem behavior, and to advise the parents accordingly.

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## GYNECOLOGY IN THE COMMUNITY\*

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PHILADELPHIA

SOME years ago a colleague of mine in a western city told me that whenever he was asked to speak on the subject of "office gynecology," he refused, because he did not believe that there was such a thing. I heartily disagree with his concept, for I think that the office of the general practitioner is often—but not always—the original source of much good for the patient.

Recently, Thompson and Thompson,<sup>1</sup> of Camden, Arkansas, presented many points worthy of cognizance and reflection, and their paper is recommended to those who have not read it. I acknowledge that it has furnished somewhat of a background for a number of things that I shall present. The authors quote a previous author, DeBakey, as follows: "There are in the United States today some 160,000 practicing physicians, of whom only slightly more than 20,000 are certified by the various specialty boards as qualified in their chosen fields." The import of this fact is that there is approximately 1 certified specialist to 8 general practitioners. Although this does not, of course, take into account part-time specialists or specialists who have not attempted to become certified, it means that the bulk of the population is taken care of, at least primarily, by the general practitioner, whose responsibility is therefore great. He must be prepared not only to recognize the gynecologic lesion that requires the specialist's attention but also to ferret out a host of disorders in every anatomic location that may require further attention by a specialist.

I admire without stint the conscientious and hard-working general practitioner, he amazes me constantly because he knows so many things about so many different regions. Any specialist, if he is not mindful of his thinking, fails to take this into account when he considers some mistake or error in judgment by the family doctor as inexcusable. How much better would he do in a field far removed from his own ivory tower? I am thankful that I am not simply a "career man" in my specialty. I cherish not only the memory of but also the experience gained in a few early years of general practice in a small community, adjacent however to an urban medical center, for this opportunity endowed me with a valuable sense of humility.

Thompson and Thompson draw attention to the fact that apparently more and more patients consider themselves competent to select their own

specialists, without consulting their family physician beforehand, and it is believed that this trend may be intensified because of the experience of war veterans and their families with the huge consultation service available in the medical departments of the armed forces—the concept is gaining ground "that only specialists are competent to treat patients."

The authors also cite Pressley's observation that "80 to 85 per cent of those seeking medical care could be skilfully and successfully cared for by a well-trained general practitioner." Although this statement may be true, it is open to contradiction far too often, as many of us know, when the physician fails to recognize his limitations. Further discussion of why this should happen is a controversial matter and has too many aspects to be covered wisely or completely in a presentation of this sort. Suffice it to say that I have merely mentioned these things as a prologue to my discussion of the part that the general practitioner in the community can take in recognizing and solving what appear to be gynecologic problems, for it is this field that I am expected to be familiar with and to offer helpful suggestions about.

Certain symptoms naturally indicate a possible pelvic complaint. Some of these should be considered serially, so that their significance and management may be fully appreciated. Generally, menstrual disturbances, pelvic pain and discomfort or annoying vaginal discharge, either alone or in combination, are mentioned primarily, too often, however, the patient soon wanders far afield, pouring out a multiplicity of complaints that may well be referable to any system in the body and are sometimes sufficient to make the diagnosis of psychoneurosis a welcome escape for the harassed listener.

## MENSTRUAL DISTURBANCES AND ABNORMAL BLEEDING

These disturbances may be in the form of amenorrhea, menorrhagia or metrorrhagia. Embarrassing indeed is the failure to consider pregnancy first when amenorrhea is complained of. I have not infrequently seen unmarried women of varying age, as well as married ones, well advanced in pregnancy in spite of a regime of estrogenic therapy. The physician should therefore inquire prudently and look well before regarding amenorrhea as a functional problem. If it apparently is one, he should not be hasty with estrogenic and allied injections, especially in the young patient not far removed

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from the onset of puberty — such treatment may do more harm than good by physiologic interference with a delicately balanced pituitary-ovarian mechanism. The general physical condition may be at fault, and medication along the lines of vitamin and ferruginous therapy may well complement wholesome reassurance and advice about diet, activity and personal hygiene. In the presence of obesity, especially of relatively recent onset, desiccated thyroid is still the most dependable endocrine product, but careful observation of tolerance to the drug is imperative. It is not always essential to estimate the basal metabolic rate before the empirical effect is noted, unless easy means for its determination is at hand. Nor is it necessary to have hormonal assays immediately in functionally amenorrheic patients. Patients falling into this category need not be referred to the gynecologist or endocrinologist until a reasonable time has elapsed with employment of the measures mentioned. When there is marked or progressive alteration in secondary sex characteristics, however, it is best to seek specialized advice, for the rare possibility of a masculinizing tumor of the ovary or a similar neoplasm of the pituitary or adrenal gland must be borne in mind.

It is well to remember that amenorrhea is only one symptom of the menopause. I cannot caution too strongly against the indiscriminate way in which estrogenic therapy is prescribed for any and all symptoms that patients may exhibit or let themselves think they must develop, when regular menstruation ceases sometimes after forty or forty-five years of age. A legend has grown up that vasomotor and nervous symptoms must develop at this time. Many a woman without such symptoms may anxiously seek endocrine therapy or even have it suggested for her, not only by friends but also by physicians themselves. Frequently, explanations and reassurance, with and without mild sedation, suffice in the management of these unpleasant vasomotor symptoms. I am inclined to believe that estrogenic therapy, employed regularly and over a long period, actually prolongs menopausal phenomena in certain cases, and we are all more or less familiar with the confusing picture produced during the postmenopausal period when so-called "withdrawal bleeding" occurs in the course of prolonged hormonal medication.

Bleeding, either menorrhagia or metrorrhagia, or both, causes most physicians a good deal of concern both in diagnosis and in management. The first point is to determine the source of the bleeding, and the next to decide whether it is organic or functional. This is sometimes difficult to do exactly, for the possibilities may overlap, owing to existing lesions combined with functional disturbance. For this reason, a careful history is essential, and the patient's decade of life is of extreme importance be-

cause of the relative frequency of causative factors likely to appear in certain age groups.

In abnormal bleeding from the genital tract in the child or the young girl approaching puberty, local causes of an organic nature, either benign or malignant, are rare, whereas constitutional or endocrine disturbances, or both, are much likelier to be at fault. Such disturbances cannot be assumed, however, until a careful pelvic examination is made in addition to a general physical survey. If a hemoglobin estimation is particularly low, a complete blood count, with bleeding and clotting times, should be taken, not only to determine any degree of anemia but also to exclude a blood dyscrasia. Tuberculosis or heart disease may be a factor, or dietetic inadequacy may be associated with metabolic disturbance and vitamin deficiency. One should not hesitate to make a pelvic survey, having excluded the general factors mentioned, before deciding on an endocrine imbalance. This can be accomplished under suitable conditions with understanding and gentleness. External viewing of the genitalia and rectal examination may be supplemented by direct inspection of the vagina through a Kelly cystoscope with reflected light or by the use of an electrically lighted instrument. Thus, a foreign body can readily be eliminated, and any peculiar lesion that might indicate a neoplasm can usually be seen if present. Bimanual rectal examination may reveal an ovarian tumor. If so, a rare feminizing tumor may be involved, although the absence of an ovarian enlargement may merely mean precocity, as Novak<sup>3</sup> has carefully pointed out. In any event, the finding of an organic pelvic lesion means that the young patient should then be referred to the specialist.

An endocrinopathy is probably the most frequent and probable cause of these disturbances. Immediate recourse to hormonal injections should be avoided. Often, these endocrine disturbances, like amenorrhea, are self-limited and respond to reassurance and general measures. Thyroid may be tried to advantage, and if it is not satisfactory, estrogen and progesterone therapy may be instituted. Testosterone may be effective as a stop-gap in the control of abnormal bleeding, but the dosage must be guarded, since the masculinizing effects of testosterone are well known. Gonadotropic hormones have been largely discarded by thoughtful endocrinologists. All in all, hormonal therapy should not be used indefinitely, for it cannot be determined with certainty what future maladjustment may result from the interference with the natural delicate endocrine balance. I have seen little good result from snake venom or styptics. If no improvement results after a reasonable trial of carefully managed endocrine therapy, the problem should be put up to the specialist, with curettage, hormonal assays and complete metabolic studies. Curettage is sometimes not only diagnostic — to

prove hyperplasia of the endometrium — but also curative for a long time, and repetition may be necessary. Even blood transfusion may have to be resorted to. Most physicians avoid irradiation in these young patients, and major pelvic surgery for functional disturbance of this nature is rarely if ever necessary. It is a wise practitioner who recognizes relatively early when he is getting nowhere with office therapy.

During the reproductive period, one is much likelier to find organic than functional causes for abnormal bleeding. First to be thought of are the abnormalities associated with pregnancy — threatened or incomplete abortion, premature separation of the placenta, or placenta previa, and ectopic pregnancy. The general practitioner doing obstetrics knows from his own experience when to seek help and is limited only by his ability to obtain such help in any of the conditions mentioned. The patient who continues to bleed from an incomplete abortion and, naturally, one suspected of harboring an ectopic gestation require reference to the specialist. In such a case it is clear thinking to consider every threatened or incomplete abortion as a possible extrauterine pregnancy.

Unhealed lacerations with eversion, erosion, polyps and subinvolution may be responsible for abnormal bleeding, and office treatment may be of great benefit. Local applications to the cervix and the use of tampons, carried out indefinitely, require time and are of no permanent value, except perhaps to the income of the practitioner. Well considered cauterization, on the other hand, is beneficial. Subinvolution, if accompanied with retrodisplacement, is often benefited by prolonged hot saline douches, the use of the knee-chest position and the judicious use of the pessary, with appropriate care in its employment. Polyps, if superficial, may be excised, and the base cauterized. The removed polyp should always be sent to a pathologist for study. I believe that the mere finding of a polyp calls for diagnostic curettage to exclude others in the uterine cavity or endometrial disease of another nature that may be a more probable cause of the bleeding, this should be a hospital procedure.

During this period one may also discover fibromyomas of the uterus and true ovarian tumors. The necessity of distinguishing between the malignant tumors and the non-neoplastic or so-called "retention cysts" of the ovary is discussed below. Naturally, lesions of the nature mentioned, if found or suspected, should be referred to the specialist for decision. The predominant thought, however, when abnormal bleeding is complained of in the reproductive period, should be of the possible existence of cervical carcinoma, and the need for early diagnosis and prompt treatment is obvious. Although the Papanicolaou vaginal-smear test may be indicative of cancer, a thorough cervical biopsy and an adequate study of the tissue by a com-

petent pathologist must be relied on to give the final answer.

Abnormal bleeding in the menopausal and postmenopausal patient may be caused by senile vaginitis, and the use of an astringent douche primarily, followed by a lactic acid douche to maintain the normal acidity of the vagina, may be all that is necessary. Estrogenic suppositories may help, but I am averse to prolonged estrogenic therapy, either by mouth or by injection, because the factor of "withdrawal bleeding" may have to be reckoned with sooner or later. Decubitus ulceration is sometimes seen in the prolapsed uterus and also occurs with irritation due to a neglected pessary. Local treatment only helps to prepare the patient for the surgical procedure that may be necessary to cure the prolapse. Nonimprovement demands biopsy, if one is to be on the safe side.

The danger signals that menopausal and postmenopausal bleeding present should be re-emphasized. The physician should not procrastinate, when such bleeding is present, even though no pelvic abnormality can be seen or felt. No local or general treatment is indicated for bleeding from the inside of the uterus. Only curettage in the hands of one qualified to carry the problem through to its final conclusion is the answer to this problem, and here again it is the pathologist who must give the final answer after careful study of the tissue. Hormonal therapy for the treatment of this symptom is not only injudicious but actually dangerous. Macfarlane<sup>3</sup> recently reported 18 cases of postmenopausal bleeding due to estrogenic therapy, with an unnecessary hysterectomy resulting in one. The physician should pass the responsibility to the gynecologist.

#### PELVIC PAIN AND DISCOMFORT

Pelvic pain and discomfort are generally associated with pelvic lesions, which may also cause referred symptoms that bring the patient to the doctor. An important thing to remember is that the presence of a pelvic abnormality, per se, does not necessarily explain the symptomatology, nor does a pelvic lesion invariably cause pain. An example is afforded by the problem of retrodisplacements of the uterus. How often is this malposition blamed as the cause of backache, and treatment instituted or operation advised, when the true cause may be found in an orthopedic or other extrapelvic lesion. Acquired retrodisplacements may cause backache but manual replacement and the use of a properly chosen pessary constitute a therapeutic test that should never be neglected before surgery is advised. Too often, surgery is recommended for congenital retrodisplacement. I do not believe that this condition is ever the sole cause of pain or discomfort unless it is complicated by pelvic inflammatory disease or endometriosis.

Renal lesions may simulate a variety of tubo-ovarian disease or appendicitis as well. The necessity of evaluating urinary findings only if the specimen obtained is a catheterized one is emphasized. Reported pus or blood in the urine may well come from a contaminating vaginal discharge should a voided specimen be relied on.

It is unfortunate that uterine carcinoma seldom causes pain until the lesion is well advanced. Vulval or primary vaginal cancer may cause pain, however, when the lesion is beginning and small in extent. Therefore, to exclude cancer, any genital sore that does not heal readily should be viewed with suspicion and biopsied promptly, as well as being studied for a venereal cause. Perhaps it is better to refer such cases promptly to a specialist.

Fibromyomas frequently cause pain and distress, and when such symptoms are investigated pelvically, either with or without bleeding symptoms, reference to the specialist for appropriate treatment is desirable. Symptomless myomas, on the other hand, may be observed at regular intervals to note their progress or regression, but the patient should always be told of their presence. This is a double protection.

Pelvic inflammatory disease of gonorrheal, postpartum or postabortal origin is usually easy to recognize, for pain is the predominant symptom. Today's treatment, with chemotherapy and particularly with penicillin, is a valuable adjunct to the conservative management that has been in vogue for so long. After subsidence of the acute symptomatology, prolonged hot saline douches and diathermy do much to help Nature in restoring the pelvic organs to normal. Rarely is surgery necessary, except in the presence of a pelvic abscess, when drainage of the cul-de-sac is indicated or when repeated attacks have occurred from time to time. Tuberculous pelvic inflammatory disease is suspected when fever and symptoms do not subside in a reasonably short time, particularly when there is an antecedent history of tuberculosis or suggestive chest findings. Pelvic endometriosis may simulate pelvic inflammatory disease, but the etiology of the latter is lacking in the history. Endometriosis presents a difficult problem in treatment. Testosterone treatment may perhaps be beneficial, if the diagnosis is an accurate one. This is not always possible, however, it must often be a presumptive diagnosis, and it is better to let the specialist decide whether or not surgery is the answer.

Ovarian enlargements are a frequent cause of pelvic pain. The responsibility of advising surgery in these cases is grave, for the primary decision is a differentiation of non-neoplastic cysts, better known as retention cysts or graafian follicle and corpus luteum cysts, and true ovarian neoplasms. Repeated examinations will help to determine this, for neoplastic growths of the ovary continue to enlarge, whereas retention cysts, being functional, tend

to alter or regress. Far too many ovaries are sacrificed by injudicious advice and by even more injudicious surgery. On the other hand, a progressively enlarging tumor demands reference to the specialist, because it may represent any variety of ovarian neoplasm, either benign or malignant. Sizeable tumors, when primarily found or when torsion of the pedicle is suspected, need prompt surgical treatment.

Finally, dysmenorrhea may be an accompanying symptom of any of the organic pelvic lesions mentioned above, but the most frequent, perhaps, is the type known as essential dysmenorrhea, which is present without demonstrable organic change, unless an acutely anteverted uterus is regarded as an organic abnormality. Although such anteversion may play a part mechanically, it is more probable that constitutional or endocrine influences, or both, and neuropsychiatric factors are to blame. I have nothing new to offer in the office control of these patients. Broad principles of management must be relied on. Reassurance and the prolonged psychosomatic approach are often necessary in addition to the correction of physical, hygienic, nutritional and environmental obstacles. Every hormonal and other remedy in the books has been tried, with testimony for and against each, by equally enthusiastic and reputable investigators — so that one can "pay your money and take your choice." Accompanying symptoms — headache, gastrointestinal disturbances and vasomotor and nervous symptoms — add to the difficulty of specific medication. Pregnancy usually relieves the trouble, but unfortunately the problem of sterility enters into the picture in some of these married patients. Antispasmodic remedies reinforced with barbiturates and codeine help the majority, the most obstinate cases should have a dilatation and curettage, or even a stem pessary. Sympathectomy is losing its popularity. I strongly believe that in the most stubborn cases, an organic lesion, particularly endometriosis, has been overlooked primarily and must be corrected.

#### ABNORMAL VAGINAL DISCHARGE

A certain amount of vaginal secretion is normal and readily explained on a physiologic basis — that is, normal glandular activity in the Bartholinian and cervical glands, with a reaction in the neighborhood of pH5 or less. It is supposed that the correlation of enzymatic activity and the presence of a normal flora in the vagina, governed by the bacillus of Doderlein, maintains normalcy. This delicate balance is readily destroyed by bacteriologic infection of varying degree.

Abnormal vaginal discharge can result from a multiplicity of causes. The most frequent is eversion of the cervical mucosa due to lacerations and accompanied by hypersecretion and low-grade infection, which may result in erosion and may be accompanied by hypertrophy and cystic degenera-

tion — the entire process being covered by the overall diagnosis of cervicitis or endocervicitis. Occasionally, one sees congenital eversion or erosion, or both, in the virgin, the result of a developmental error — based on failure of the hypertrophied cervical mucosa, stimulated in utero by the mother's estrogens, to regress at birth.

Next in frequency is the discharge due to gonococcal infection, which involves Skene's tubules, Bartholin's glands and most frequently and persistently the glands of the cervical canal. Secondary irritation of the vagina and vulva then follows, and a profuse and offensive discharge results.

Often seen and readily recognized in a wet smear is a *Trichomonas vaginalis* infection, which is often due to the prolonged activity of this flagellate in an unhealthful environment, as noted above. The primary source of this organism is still a moot question, but its presence is associated with a most annoying and irritating discharge. Yeast fungi, principally of the *Monilia* group, act in a similar fashion.

Discharges, of varying degrees and amount, of course, accompany serious lesions, principally carcinoma of the external genitalia and uterus due to secondary infection of necrotic tissue. Pyometra, caused by cervical-canal stenosis, cancer or degenerating myomas, also falls into this group. Pruritus based on metabolic disorders, such as diabetes, and giving rise to local irritation and itching may also be accompanied by discharge. The breakdown of venereal and granulomatous lesions or of tuberculous ones has a similar effect.

The principal responsibility of the general practitioner is to try to recognize the cause. In the group mentioned above it is obvious that reference to the specialist is desirable in most cases, especially when a possible neoplasm exists.

In the treatment of a discharge associated with acquired eversion of the cervical canal, douches and local applications require time and are usually inadequate. The nasal-tip cautery, however, may be employed as an office procedure, provided there is no acute infection as evidenced by a history of possible gonorrheal infection, the presence of fever and the existence of pelvic inflammatory disease, as determined by bimanual examination. In cases in which marked hypertrophy and extensive cystic degeneration are present, however, endothermic resection or a plastic operation — both of which are essentially hospital procedures — had better be employed.

Of especial benefit is the light cauterization of the congenital type of eversion, which can be accomplished in the virginal girl by exposure of the cervix with a small speculum or Kelly cystoscope but is frequently impossible because of the young patient's natural sensitivity, and it is necessary to carry out the treatment under anesthesia as a hospital task. In all cases of cervical cauterization subsequent

dilatation of the cervical canal is desirable at indicated intervals to lessen the incidence of atresia or stenosis, a sterile uterine dressing forceps can be used effectively. Lactic acid douches may be advised after complete healing has taken place.

When *T. vaginalis* infections are discovered, it is perhaps better to clear up any abnormalities that exist to ensure less likelihood of recurrence, although it is quite permissible to attack the infestation primarily to promote symptomatic relief. The remedies employed are legion, the important thing to remember is to attempt to restore the normal flora of the vagina as quickly as possible. I prefer the use of silver picrate, by insufflation and suppository, first to destroy the trichomonads, the reaction being maintained thereafter by the regular use of lactic acid douches (a teaspoonful to 2 quarts of warm water). In persistent cases infection of the urinary tract and a partner harboring the organism in the prostate gland should be sought. *Monilia* infestations are handled in almost similar fashion, with a keen lookout for an excess of sugar in the blood or urine, or both.

Discharge due to gonorrheal infection may be due to the initial attack, to recurrence or to chronic infection of Skene's tubules, Bartholin's glands or the cervical glands. Smears and cultures are helpful, but may not give positive results. In any event, if the history and clinical findings are sufficient to warrant a presumptive diagnosis, local measures should be avoided in the acute and subacute stages, chemotherapy and penicillin being depended on. Later, chronic infection may be eradicated with the cautery or endotherm, Skene's tubules and the Bartholinian glands being also regarded as foci. If gonorrheal infection has ascended beyond the cervix, as indicated by evidence of pelvic inflammatory disease on bimanual examination, one should by all means go slowly in prescribing local treatment. In such cases chemotherapy and penicillin are of little help, and the physician must wait for further subsidence of the inflammatory process before resorting to anything else. Later, cleansing douches, particularly prolonged hot saline douches, will be found most helpful in restoring the pelvis to normal or in alleviating pain and menstrual disturbance. The question of subsequent surgery, because of organic or functional disability or because of repeated attacks, is for the specialist to decide.

#### INFERTILITY

Finally, regarding the problem of the barren marriage, I must speak cautiously, for I am within the very citadel of research and wisdom that pertains to infertility. Fortunate is the practitioner of New England, who can send his problems to Boston!

The couple who seek advice should be persuaded that any studies must be on a partnership basis. The husband must be excluded as the partner at fault, if possible. His role is lessened. Only if no

organic disease can be detected in the woman's pelvis is a tubal insufflation test indicated, the examiner should beware of telling the woman that she has a "tipped womb" and can never conceive, for his face may be red nine or ten months later. Proceptive advice, especially concerning the ovulatory period, may be given and practiced even before tubal insufflation. The physician should depend on desiccated thyroid before resorting to a galaxy of hormonal injections, and should not

overlook constitutional defects in either partner. If after a reasonable trial of sane advice and simple measures along these lines, he believes that he has failed, he should seek counsel of the specialist — who may do no better.

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### Q FEVER\*

#### Report of a Case

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THE speed of modern travel and the relatively long incubation period of many infectious diseases have made it necessary for the physician to have some acquaintance with global epidemiology, to cope with some of his diagnostic problems. In the case reported below a diagnosis of Q fever was established serologically in a patient with clinical findings of primary atypical pneumonia. The diagnosis was suspected from the fact that the patient had been in an area where the causative agent of the disease occurs and had returned from that area within the known incubation period of the disease.

I. M., a 56-year-old merchant, became ill on March 3, 1947 while on a transatlantic steamer returning to the United States from a 3 month business trip in Europe. The illness began suddenly with chills, generalized aching anorexia, malaise, dizziness and slight diarrhea. There was also a slight cough without pain. The patient was seen on the same day by the ship's physician § who found the temperature to be 103.8°F., the pulse 116, and the respirations 36. Examination revealed no abnormal findings except "slight respiratory roughness on auscultation." Urinalysis then showed a slight amount of albumin. The temperature on the following day dropped to 99.8 F., but on March 5 was again found to be 103.4 with a pulse of 110 and a respiratory rate of 40. Meanwhile the patient continued to cough and he raised small amounts of blood flecked sputum. He was given fluids liberally some "pills" (probably aspirin) and two injections of penicillin in-oil during these 2 days without benefit. He felt comfortable except that he perspired profusely especially after taking the pills. The ship docked in New York on March 5, and the patient came directly to Boston by plane and was admitted to the Beth Israel Hospital on the following day. He had no pleural pain or headache and had not noted any blood in the stools.

The patient had had diphtheria at the age of 10 but gave no other history of infectious diseases. He was known to have had slight hypertension for a number of years. He had also had frequent colds but none that were severe. For the past several years he had noted occasional subnormal pressure on exertion that was relieved by belching.

Physical examination revealed a well developed and somewhat obese patient. He was well oriented but appeared acutely ill and feverish, perspiring profusely, breathing rapidly, coughing frequently and raising small amounts of tenacious blood streaked and rusty sputum. Examination of the chest revealed limited expansion of the right side. Over the lower half of the right portion of the chest posteriorly there was moderate dullness with numerous medium crepitan rales at the end of inspiration and after coughing some coarse rhonchi on expiration and diminished tactile fremitus, spoken voice and breath sounds. The left lung was normal. There were no skin lesions, the spleen was not felt, and the rest of the physical examination revealed no abnormalities.

The temperature was 104 F., the pulse 108 the respirations 38 and the blood pressure 138/86.

The patient was given 50,000 units of crystalline penicillin G in aqueous solution intramuscularly every 3 hours until March 13. He also received 8 cc. of elixir of terpin hydrate with codeine every 4 hours for 3 days after which the drug was discontinued because of nausea and epigastric distress. No other medication was given. The temperature chart is presented in Figure 1. The patient continued to sweat profusely until the temperature reached normal. The cough continued throughout the febrile period and then abated. The sputum was blood tinged until March 9 thereafter it was mucopurulent and scant and no sputum was raised after March 11. The patient appeared to be quite comfortable and cheerful throughout most of his hospital stay except for some restlessness at night during the height of the fever. His appetite remained poor during the febrile period but began to improve after March 9. Epigastric distress was present from the time of admission until March 11. After the temperature reached normal the patient began to improve rapidly although the physical signs in the lungs remained essentially unchanged until discharge from the hospital on March 19.

X-ray examination of the chest on March 6 revealed findings that were consistent with a segmental pneumonia in the anterior and lower portions of the right lower lobe with an associated atelectatic component. The configuration of the heart and aorta suggested hypertensive heart disease. On March 8 the consolidation of the right lower lung was somewhat smaller in extent. Films taken 3 days later showed a further decrease in the extent of consolidation at the right base and no new abnormalities. The roentgenograms and

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§We are indebted to Dr. J. B. Margule, medical officer of the *Queen Elizabeth* for an abstract of his record of this case.

fluoroscopic findings on March 17 also indicated a further decrease in the extent of the segmental consolidation in the right lower lobe. There was definite evidence of retraction of the interlobar fissure, suggesting a persistent atelectatic component in the pneumonic consolidation at that time. Re-examination on May 12 showed almost complete re-aeration of the right lower lobe, with only a small triangular area of consolidation adjacent to the anterior interlobar fissure. The lung fields were otherwise clear. Both leaves of the diaphragm were in normal position and showed normal excursion by fluoroscopy. The anteroposterior and lateral views of the chest on March 6 and on May 12 are presented in Figure 2.

Urinalysis on admission showed a ++ test for albumin and a rare white blood cell in the sediment but 2 days later was negative. Examination of the blood revealed a red-cell count of 4,610,000, with a hemoglobin of 13.0 gm per 100 cc, and a white-cell count of 11,500, with 72 per cent neutrophils, 22 per cent lymphocytes, 5 per cent monocytes and

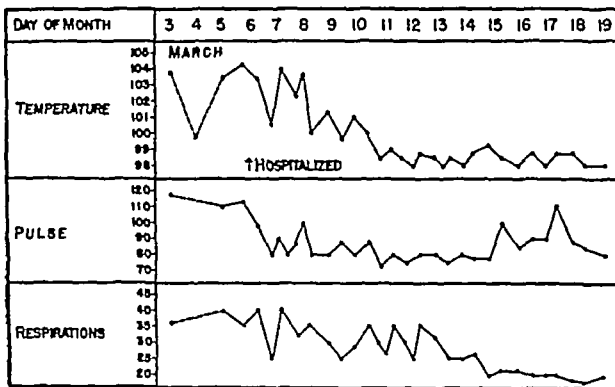


FIGURE 1 Clinical Chart

1 per cent eosinophils. On the following day the white-cell count was 11,600, with 84 per cent neutrophils, 10 per cent lymphocytes and 6 per cent monocytes. A few of the neutrophils showed toxic granules. The sputum showed gram-positive cocci in pairs and chains and no acid-fast bacilli in the stained smears, and cultures showed a predominance of alpha-hemolytic streptococci. Blood cultures taken on admission were negative. Cultures of the stools on March 9 and 10 yielded no pathogenic organisms. The serums on March 7 and 19 were negative for typhoid and paratyphoid agglutinins. Tests for cold agglutinins and for antibodies against influenza A and B viruses (Hirst test) on serums obtained on March 11 and 19 and April 30 were negative. An electrocardiogram taken on March 13 was suggestive of an old anterior myocardial infarct, but no changes of significance were noted in later electrocardiograms.

Complement-fixation tests for Q fever were carried out with the patient's serum by Dr. Herald R. Cox, of the Section of Viral and Rickettsial Research of the Lederle Laboratories. The strain used in these determinations was the original American strain isolated from *Dermacentor andersoni* at the Hamilton, Montana, laboratory of the United States Public Health Service and was originally called the "Nine-Mile Strain". The results were reported as follows: March 11, ++++ in a dilution of 1:16, March 19, ++++ in a dilution of 1:128, and April 30, ++++ in a dilution of 1:256 and ++ in a dilution of 1:512. These results indicate that the patient undoubtedly had Q fever.

The essential features of this case were the sudden onset with chilly sensations, anorexia, cough and mild diarrhea, the temperature of 102 to 104°F with a relatively slow pulse for six days, gradual defervescence between the sixth and ninth days, marked sweating throughout the febrile period,

increased at first by antipyretics, marked to moderate cough productive of small amounts of blood-streaked and rusty sputum throughout the febrile period, an increased respiratory rate without dyspnea, moderate to mild illness with only occasional periods of restlessness during the height of the fever, physical and roentgenographic evidence of atypical pneumonia and segmental atelectasis limited to the right lower lobe with residual x-ray findings in that area after more than two months, absence of pleural pain, rash or palpable spleen, slight neutrophilic leukocytosis, negative cultures for pathogenic organisms in the blood, sputum and stools, negative serologic findings for enteric agglutinins, cold agglutinins and for the viruses of influenza A and B, and, finally, a significant and progressive increase in the titer of complement-fixing antibodies for the rickettsia of Q fever after the middle of the second week of the disease, the titer remaining elevated after the eighth week.

*Rickettsia burneti*,<sup>2</sup> the causative agent of Q fever, has been recovered under natural conditions, either in infected ticks or from human cases, in Australia,<sup>3</sup> in several western states in this country from Texas to Washington,<sup>4</sup> in Italy,<sup>6</sup> in the Balkans<sup>6</sup> and in Panama.<sup>7</sup> An outbreak among troops in Camp Patrick Henry, Virginia, originated in Italy.<sup>8</sup> In Australia, Q fever is essentially an occupational disease affecting chiefly slaughterhouse workers, dairy hands and foresters.<sup>3</sup> The recent outbreak in Amarillo, Texas, involved stockyard and packing-house workers.<sup>9</sup> Several outbreaks have been described among personnel in laboratories where work with the agent was carried out,<sup>10-14</sup> and at times affected persons who had not had direct contact with the agent. Infection in most cases is presumed to be by inhalation of infected materials. There was a history of a tick bite in some American cases that occurred in areas where the rickettsia of Q fever has been found.<sup>4</sup> The exact mode of transmission of the disease to human beings, however, is not known.

Pulmonary lesions have not been recognized as a prominent feature of Australian Q fever. The signs and x-ray findings of atypical pneumonia were first described in the outbreak at the National Institute of Health.<sup>10</sup> They were an important feature of the first authenticated case that was naturally acquired in this country<sup>15</sup> and in the various groups of cases studied by the Army units,<sup>7, 11, 12, 16, 17</sup> as well as in the Amarillo outbreak.<sup>18</sup>

The findings shortly after admission in the case reported above were those of a primary atypical pneumonia. A brief survey of the itinerary of the patient indicated that he had been in Italy in the vicinity of Naples for two or three weeks before the onset of symptoms. The possibility of Q fever was therefore immediately suspected on the basis of the reports of the occurrence of that disease in

association with atypical pneumonia in this region and in other parts of Italy. Suspicion was further

stored in supply depots in that vicinity. Although he was not aware that any of the buildings that he



FIGURE 2. X ray Films of the Chest on March 6 (above) and on May 12 (below)

increased when inquiry revealed that the patient had spent about ten days in the vicinity of Naples inspecting United States Army stocks that were

visited had been used for housing livestock, such a possibility could not be excluded. Most of the military cases reported from that area occurred



crucial value of spinal anesthesia — the status of the gastric contents is not of vital importance if spinal anesthesia is employed. It is also strongly believed, as mentioned above, that the risk is markedly increased as the dosage is increased and that the reported deaths under spinal anesthesia were a result of excessive dosage.

There were no permanent neurologic sequelae. This feared complication must be recognized as a potential hazard but should not be distorted out of all proportion. Shimberg<sup>9</sup> investigated 14,073 patients receiving spinal anesthesia at a Veterans Administration hospital and reported 2 cases of nonspecific meningitis and 3 cases of peripheral neuritis. These were transient, with no permanent paralysis or loss of sensation. Stein and Tovell<sup>10</sup> state that in a series of over 10,000 patients receiving spinal anesthesia at the Mayo Clinic no permanent motor paralysis has been encountered. The risk is present, but the incidence of this complication does not justify the exclusion of a valuable method of anesthesia.

There can be little doubt that any method of regional anesthesia has the least harmful effect on the fetus. Effects on fetal respirations are a result of one or more of the following factors:

**Premedication** The use of regional anesthesia has conclusively proved that sensible, conservative premedication with the barbiturates and scopolamine has no deleterious effect on the fetal respirations. Morphine sulfate has been employed in a small number of cases when deemed advisable, and even this dreaded obstetric narcotic has exerted little if any influence on the fetal respiration when spinal anesthesia was used.

**Anesthetic drug** The volatile liquid inhalation agents, such as ether, chloroform and vinethene, and the gases, such as cyclopropane, ethylene and nitrous oxide, are capable of exerting their effects on the fetus. Pentothal Sodium also enters the fetal circulation and can narcotize the fetus, but 50 mg of procaine deposited in the spinal canal has thus far demonstrated no effect on fetal respirations.

**Hypoxia** No inhalation agent permits the use of 100 per cent oxygen in the inspired mixture at all times. Nitrous oxide and oxygen is notoriously prone to produce hypoxia, and this is in fact necessary to a certain extent to produce anesthesia of the third plane. The other inhalation agents vary only in the extent of oxygen deprivation. This hypoxia is transmitted to the fetal brain. It is pertinent to make special mention of cyclopropane, whose proponents have always stressed the high concentration of oxygen that can be permitted with this drug. It is well to caution that the amount of oxygen flowing into a closed system does not indicate the blood saturation with oxygen. Cyclopropane, with its

lack of respiratory stimulatory effect, does not ensure against hypoxia even though the mixture contains 80 or 90 per cent oxygen. The drug can also enter the fetal circulation and depress the respiratory system with resulting fetal anesthesia, hypoxia and brain damage. Great care must be exercised if cyclopropane is used, so that this complication is not encountered.

Only with the employment of regional methods of anesthesia or in the absence of anesthesia can one be sure that the maternal respirations are affected to the least possible degree. In the event that they are altered 100 per cent oxygen can be administered for an indefinite period without affecting the anesthetic intensity or depth. The routine use of oxygen is advocated during the period of actual delivery.

A discussion of the general indications and contraindications of spinal anesthesia is not warranted here. The only obstetric contraindication is the decision to perform an internal podalic version, in which uterine relaxation is mandatory. Cleland's<sup>11</sup> neurologic study has shown that regional anesthesia limited to the spinal nerves below the tenth thoracic segment will not interfere with uterine tone or contractility. Therefore, it is not suitable in this obstetric maneuver, unless larger dosages of spinal anesthesia are employed. Deep ether is preferred. All other types of delivery can be performed under spinal anesthesia.

No discussion will be entered into regarding spinal anesthesia in cesarean section except to state that it was employed in all sections performed at the Army Air Forces Regional Hospital. The procedure carried no mortality or morbidity and was the method of choice.

The satisfactory and safe employment of spinal anesthesia is considered to depend chiefly on the following factors, which must be rigidly adhered to: the first and most important is the administration of a small amount of anesthetic drug, such as 50 mg of procaine; the second factor is the introduction of the drug at a low level — that is, the third or fourth lumbar interspace; finally, ephedrine sulfate must be administered just prior to the anesthesia.

It is our opinion that spinal anesthesia has the following advantages in obstetrics: completely painless delivery, complete control over progress of the delivery by the obstetrician, complete relaxation of the perineum, elimination of an inhalation anesthetic and thus a lower incidence of pulmonary complications, no distortion of the perineum by injection of local anesthetic agents, absence of fetal depression due to anesthesia, and suitability for use on patients on whom general anesthesia is contraindicated — that is, its wide range of application.

#### SUMMARY

A series of 595 patients delivered by the pelvic route under spinal anesthesia is presented. The

technic is outlined, and the results obtained are discussed

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## MEDICAL PROGRESS

### CURRENT CONCEPTS OF JAUNDICE, WITH PARTICULAR REFERENCE TO HEPATITIS (Concluded)\*

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#### INFECTIOUS AND SERUM HEPATITIS‡

The etiology of infectious hepatitis, like that of yellow fever, long remained a mystery, owing to a lack of susceptible experimental animals. During the war years, however, it was demonstrated by studies on human volunteers that the agent responsible for outbreaks of acute hepatitis is filterable and that it is present in the blood and stools and perhaps occasionally in the urine and nasopharyngeal washings of infected persons.<sup>47-54</sup> Since it now appears that transmission occurs for the most part by fecal contamination,<sup>55-57</sup> and since ordinary chlorination of water fails to inactivate the agent,<sup>58</sup> it is imperative that patients with infectious hepatitis be subjected to isolation precautions similar to those employed in typhoid fever and dysentery, and that the disease be made reportable to public-health authorities.<sup>59, 60</sup> Whether or not transmission also occurs by nasopharyngeal secretions remains an unsettled question.

The term "homologous serum jaundice" arose when it was learned that persons receiving pooled human serum or plasma, even in doses as small as 0.01 cc., were subjected to considerable risk of developing hepatitis.<sup>52, 61-64</sup> This was found to be true regardless of the form in which the serum or

plasma was given. Jaundice was observed after the administration of measles and mumps convalescent serum,<sup>65-69</sup> yellow-fever vaccine containing human serum,<sup>70, 71</sup> pappataci-fever vaccine,<sup>72</sup> and liquid and reconstituted dried serum and plasma,<sup>73-75</sup> and also after transfusions of whole blood.<sup>76, 77, 78, 79</sup>

Freezing, drying and storing do not seem to alter the icterogenic properties of plasma and serum.<sup>80</sup> It is possible that the process of fractionation of plasma also fails to inactivate the hardy agent of hepatitis. In fact, absence of jaundice in the thousands of persons injected with gamma globulin prepared from large pools of adult plasma can perhaps best be explained by the presence of specific antibodies in this fraction.<sup>81</sup> The prevention and attenuation of infectious hepatitis has actually been accomplished by administration of gamma globulin in controlled studies,<sup>82-85</sup> but attempts to prevent homologous serum jaundice by this method have thus far yielded equivocal results. There have been no reports of hepatitis attributable to administration of normal serum albumin, another product of large-scale fractionation,<sup>86</sup> but the lack of such reports may be due to difficulties in conducting follow-up studies.<sup>87</sup>

Since the icterogenic agent may be present in high titer in the blood of infected persons, and since only a small portion of donors are infective, the hazard of jaundice may be increased as the number of donors contributing to the pool is increased, provided specific antibody from some contributors to the pool is not present in amounts sufficient to neutralize the agent.<sup>88, 89</sup> If a single donor is infected, the serum or plasma that he contributes may contaminate the entire pool. Although the period

\*Presented in part at the annual meeting of the Vermont State Medical Society, Burlington, Vermont, October 4, 1946, and at a joint meeting of the Council of Rochester Regional Hospitals and the staff of the Veterans Administration Hospital, Bath, New York, November 14, 1946.

†In the preparation of this material no attempt has been made to include a complete review of the many controversial aspects of normal and abnormal bile-pigment metabolism. The aim has been merely to present, with illustrations, concepts that seem currently to be most acceptable and most contributory to an understanding of the pathogenesis of jaundice.

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§More complete reviews of the literature on infectious hepatitis and serum hepatitis have recently been presented by Hardy and Feinstone<sup>90</sup> and by Nefz.<sup>91</sup>

¶In a paper that appeared after the preparation of this study, Spurling, Shaw and Vaughan<sup>92</sup> reported an incidence of 7.3 per cent in 2019 patients receiving transfusions of pooled human serum or plasma. Definite jaundice did not develop within a five-month period of observation in any of 1284 patients given whole blood or in any of 1284 control patients who received no transfusions.

¶Jancway<sup>93</sup> states that during the processing of albumin it is now possible to treat it with heat for ten hours at 60°C., thus exceeding the thermal death time of a well studied strain of serum hepatitis virus. The same caution has been taken even though there have been no known cases of hepatitis that could reasonably be attributed to the injection of any products of plasma fractionation.

of infectivity of hepatitis has not been conclusively established,<sup>90</sup> it is now realized that in the selection of donors for the preparation of serum or plasma or for any type of transfusion, care must be taken to exclude those who have had jaundice, exposure to infectious hepatitis or transfusions or injections of blood, plasma or serum within the preceding year.<sup>64, 84, 91</sup> Donors who constitute the greatest threat are those in the preicteric stage of hepatitis and those who have hepatitis without jaundice.

The exact relation between homologous serum hepatitis and naturally occurring infectious hepatitis

TABLE 1 Comparison of Infectious Hepatitis and Serum Hepatitis

CHARACTERISTICS	INFECTIOUS HEPATITIS	SERUM HEPATITIS
<b>Etiologic agent</b>		
Filterable	Yes	Yes
Resistant to heating, freezing and drying	Yes	Yes
Pathogenic for man only	Yes	Yes
Disease transmitted by administration* of		
Serum (P, O, N)	Yes	Yes
Stool (P, O, N, G)	Yes	No
Duodenal washings (O)	Yes <sup>92</sup>	No reports
Urine (O, N)	Irregular <sup>92</sup> "	No reports
Nasopharyngeal washings (N)	Irregular <sup>92</sup> "	Irregular <sup>97</sup> "
Disease spread by personal contact or by fecal contamination of food and water	Readily	Rarely <sup>98</sup>
Incubation period	14-35 days†	40-160 days†
Pathology	Same as that of serum hepatitis	Same as that of infectious hepatitis
<b>Clinical features</b>		
Attack confers immunity to infectious hepatitis‡	Yes <sup>94</sup>	No <sup>97</sup> "
Attack confers immunity to serum hepatitis	No <sup>94, 95</sup>	Yes <sup>94</sup>

\*The routes of administration are indicated as follows: P = parenteral, O = oral, N = intranasal (and in certain cases, intrapharyngeal), and G = gastric.

†Reported incubation periods in a few cases fall outside the ranges given. Neefe et al.<sup>96</sup> have shown that the period between inoculation of icterogenic serum or plasma and the first manifestations of hepatitis may be as short as twelve to thirty-five days, although clinical jaundice may not appear until much later.

‡A possible example of heterologous immunity is cited by Oliphant,<sup>99</sup> who produced typical homologous serum jaundice in 4 of 11 volunteers inoculated with serum from a patient with naturally occurring infectious hepatitis, no jaundice developed in 10 inoculated control subjects who had previously had homologous serum jaundice.

is not yet settled.<sup>92</sup> From the comparison presented in Table 1, it is apparent that there are at least two types of hepatitis virus that are immunologically distinct and that their incubation periods differ sharply. It is also significant that stools from patients with serum hepatitis have thus far proved noninfective when administered to human volunteers. Stools from patients with naturally occurring infectious hepatitis, on the other hand, have proved infective in a high percentage of trials. Despite these important differences, it seems likely that infectious hepatitis and serum hepatitis are caused by filterable viruses that are closely related and that the agent of serum hepatitis has been modified

through passage from person to person by artificial means.

Neefe, Gellis and Stokes<sup>94</sup> emphasize the fact that both the virus of serum hepatitis and that of infectious hepatitis can be transmitted by blood, plasma and serum. If the term "homologous serum hepatitis" is applied to all cases developing after the injection of blood products, the two types of viruses must be kept in mind. It must also be appreciated that both viruses can probably be transmitted by the use of unsterilized syringes and needles in the drawing of blood or the injection of any type of substance.<sup>99-102</sup> Transmission is particularly apt to occur in this way when diagnostic, therapeutic or prophylactic procedures are carried out on large groups of people, as in diabetic<sup>103</sup> and syphilitic clinics.<sup>94, 99, 104-109</sup> It seems likely, in fact, that a considerable number of patients who develop hepatitis during the course of antisiphilic therapy are actually suffering from syringe-transmitted virus hepatitis rather than from the toxic effects of arsenical drugs on the liver. The extent to which arsenic modifies the response of the liver to viral invasion is unknown.<sup>110</sup>

Recent observations by Lucké<sup>111</sup> and others<sup>112-114</sup> confirmed Eppinger's<sup>115</sup> earlier reports that so-called "catarrhal jaundice" is in most cases primarily a hepatitis, the principal lesions in fatal cases being those of acute yellow atrophy. The reported pathological findings in infectious hepatitis are essentially the same as those observed in serum and arsenotherapy hepatitis. Lucké<sup>111, 116</sup> emphasizes the facts that less than 0.5 per cent of cases of epidemic hepatitis terminate fatally and that most patients make a complete and apparently permanent recovery.\* There remain, nevertheless, a certain number of patients who survive the initial attack but continue for months or years to have clinical evidence of liver injury. The exact nature of the pathologic processes that take place and the relation between acute hepatitis and cirrhosis are not entirely clear.<sup>28, 29, 34, 118-120</sup>

Bloomfield<sup>28</sup> suggests that the clinical course of hepatitis may be analogous to that of glomerulonephritis so far as latency and chronicity are concerned. Lichtman<sup>121</sup> states, moreover, that in various studies of cirrhosis it is estimated that in 6 to 32 per cent of patients the cirrhotic process may have been initiated by an attack of acute hepatitis. The difficulties in making such estimates are obvious, however, in view of the facts that hepatitis may occur without jaundice<sup>23, 122, 123</sup> and that many cases of hepatitis without clinical icterus have, no doubt, been incorrectly diagnosed as influenza or gastroenteritis. Diagnostic difficulties and other factors, particularly diet, must be taken into account in any evaluation of the relation between acute hepatitis and cirrhosis. It is hoped

\*Although the mortality in epidemic hepatitis is uniformly low, that in homologous serum hepatitis is variable. A high mortality from serum hepatitis has been reported, particularly among wounded men.<sup>117</sup>

that more information on the incidence and pathogenesis of latent, recurrent and chronic hepatitis or cirrhosis will be forthcoming during the next decade as a result of follow-up studies on patients who contracted hepatitis, either naturally or by experimental inoculation, during World War II

#### LABORATORY TESTS FOR BILIRUBIN AND UROBILINOGEN

The several laboratory tests for hemoglobin derivatives that are most useful in the differential diagnosis of jaundice are worthy of brief comment.

The icteric index, which is determined simply by the matching of serum with standard solutions of potassium bichromate, provides a rough estimate of the degree of bilirubinemia. It does not, however, distinguish between bilirubinglobin and free bilirubin or between bilirubin and the yellow color due to hychromes, carotene and other substances, which are differentiated by the quantitative van den Bergh determination. The qualitative van den Bergh test has inherent faults, but the adaptation of this reaction by Malloy and Evelyn<sup>124</sup> for the measurement of serum bilirubin with the photoelectric colorimeter has proved to be of distinct value. According to Ducci and Watson,<sup>125</sup> the color that develops within a minute after serum and diazo reagent are mixed—that is, the direct one-minute value—is a quantitative expression of the qualitative prompt direct van den Bergh reaction, presumably owing to the presence in the serum of free bilirubin or sodium bilirubinate. The color that develops within fifteen minutes after serum is mixed with diazo reagent in addition to 50 per cent methyl alcohol is a measure of the total bilirubin—that is, bilirubinglobin and free bilirubin. The difference between the two values probably measures the amount of bilirubinglobin—the so-called “indirect type” of bilirubin—present in the serum. In retention jaundice the direct reading comprises a relatively small fraction of the total bilirubin present, and in obstructive jaundice, the reverse is true, and in the presence of hepatocellular necrosis, variable proportions may be found. Actually, the proportions of the two types of bilirubin present in the serum may fluctuate widely during the course of a single illness. This is particularly true in hepatitis, owing to varying degrees of cellular damage, intrahepatic biliary obstruction and cholangiolitis.

The upper limits for the direct fraction and for total serum bilirubin in subjectively healthy persons are approximately 0.2 mg and 1.0 mg per 100 cc.,\* respectively.<sup>127-129</sup> The ratio of icteric index to total serum bilirubin concentration in milligrams per 100 cc. cannot be stated accurately, especially for the normal and lower pathologic ranges. Accord-

ing to data available in the literature, the ratio may vary from 5:1 to 10:1, depending on the degree of hyperbilirubinemia, the chemical methods of measurement and, possibly, the proportions of the two types of bilirubin present.<sup>127-129</sup> Serum with an icteric index of 100, for example, might be expected to have a total serum bilirubin concentration of from 10 to 20 mg per 100 cc. In the laboratories of the Strong Memorial Hospital the ratio has varied from 5:1 to 8:1 in the higher pathologic range and from 7:1 to 13:1 in the normal and lower pathologic ranges.

Examination of the stool is of the utmost importance in following the course of patients with jaundice. The pale or clay-colored stool, which is found in the presence of regurgitation jaundice, contains excessive amounts of fat and little or no urobilinogen. Diminution in the flow of bile impairs fat digestion and absorption, and since only small amounts of sodium bilirubinate are excreted into the duodenum, the amounts of urobilinogen found in the feces are correspondingly low. Gross inspection of the stool is essential but sometimes misleading because excessive fat may mask the presence of significant amounts of urobilinogen or urobilin.<sup>13</sup> On the other hand, food pigments may give a brown color to stools containing little or no urobilinogen or urobilin.<sup>131</sup> Watson and his associates<sup>122</sup> have recently developed a simplified method for determination of the per-diem excretion of urobilinogen in the feces. It is admittedly crude, compared with more elaborate methods involving extraction with petroleum ether,<sup>122</sup> but it is sufficiently accurate to indicate trends in pigment excretion and sufficiently simple to be carried out quickly by inexperienced personnel. Fecal bilirubin is seldom measured in clinical studies because it escapes reduction to urobilinogen only in the presence of diarrhea and in newborn infants, in whom intestinal bacteria are not yet established.<sup>13</sup>

The simplified method for the determination of urobilinogen is also applicable to the urine.<sup>122-131</sup> Serial tests of twenty-four-hour specimens or of samples collected between 2:00 and 4:00 p.m. are most useful and can be carried out in a few minutes. The significance of variations in urinary urobilinogen excretion is pointed out below. The foam test for bilirubinuria requires no reagents or equipment but is less sensitive and less specific than Harrison's test.<sup>132-136</sup> Watson and Hawkinson<sup>137</sup> have recently described a semiquantitative modification of Harrison's test that appears to have merit. Strips of thick retentive filter paper impregnated with barium chloride are dipped in urine and then dried, and a mixture of trichloroacetic acid and ferric chloride is applied to oxidize the bilirubin to biliverdin. The depth of the resulting green color is compared with standards to give the approximate concentration in milligrams per 100 cc. This test has the additional advantage of convenience since the two materials

\*Sometimes higher figures for total serum bilirubin concentration are obtained by the method of Jendrassik and Grof<sup>124</sup> which Wirth<sup>127</sup> prefers to that of Malloy and Evelyn.<sup>124</sup> Ducci and Watson<sup>125</sup> attribute the lower values obtained by Wirth for the Malloy-Evelyn procedure to the use of alkali which was not recommended by Malloy and Evelyn.

required, the impregnated paper strips and the oxidizing agent, are easily prepared and usable for long periods<sup>138</sup> The Gmelin, iodine, methylene blue<sup>138-141</sup> and other tests<sup>135, 142</sup> for bilirubinuria that have been described are less sensitive than Harrison's test and require no further comment

DIFFERENTIAL DIAGNOSIS

The illustrations presented below will serve to indicate how determinations of bilirubin in the

bilirubinuria are negative, but the amounts of urobilinogen found in the urine may be considerably increased if the liver is unable to re-excrete the large quantities absorbed from the colon In acute hemolytic processes, such as blackwater fever, red cells may be destroyed intravascularly, and the liberated hemoglobin may be excreted in the urine if the renal threshold is exceeded. If hemolysis is extensive, part of the hemoglobin may be broken down to hematin, which then unites with albumin

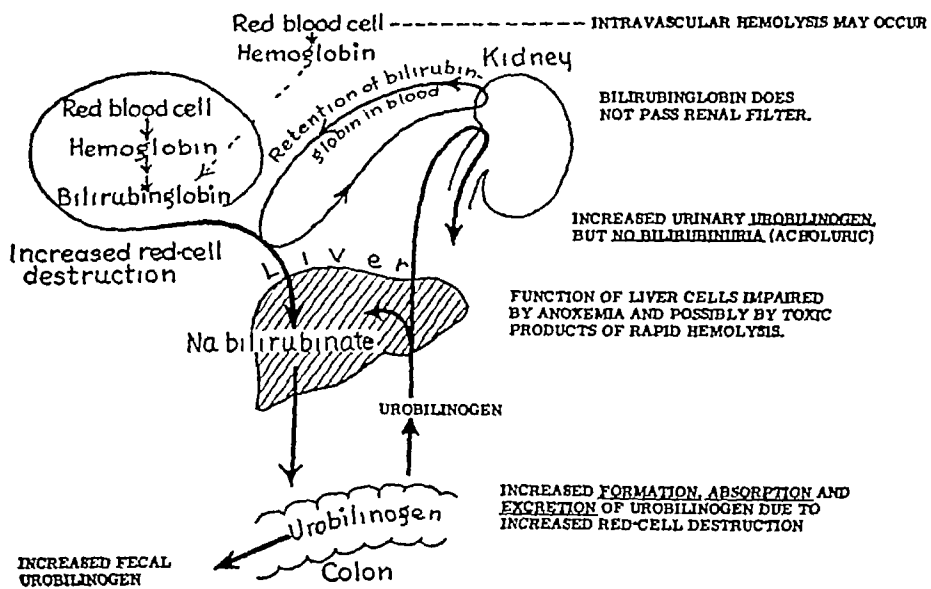


FIGURE 11 *Abnormalities of Bile-Pigment Metabolism in Retention Jaundice Associated with Hemolytic Anemia*

blood and urine and of urobilinogen in the urine and stool may be helpful in the differential diagnosis of jaundice

Figure 11 shows by means of heavy arrows that in hemolytic anemia increased red-cell destruction results in increased formation of bilirubinglobin, sodium bilirubinate and urobilinogen. The entire red-cell mass may, in fact, be turned over every few days<sup>143, 144</sup>. Despite certain difficulties inherent in its measurement, increased excretion of urobilinogen in the feces is considered the most reliable index of rapid erythrocyte breakdown<sup>145, 146</sup>. Urinary urobilinogen excretion is also increased as a rule during hemolytic processes, but the amounts found in the urine are subject to wide variation, depending on the extent to which urobilinogen is absorbed from the colon and metabolized by the liver. In patients with hemolytic anemia the function of the liver cells is impaired by anoxemia and probably by other factors, with the result that a portion of the excess bilirubinglobin delivered to the blood and carried to the liver from the reticuloendothelial system is retained in the blood. Since bilirubinglobin does not pass the renal filter, hemolytic jaundice is often referred to as acholuric jaundice. Tests for

to form methemalbumin, an apparently toxic substance. A large portion of the liberated hemoglobin, however, is picked up by the reticuloendothelial system and converted to bilirubinglobin in the usual way<sup>17</sup>.

Figure 12 indicates that, in cases of constitutional hepatic dysfunction, the only abnormality appears to be the retention of bilirubinglobin in the blood due to functional impairment of liver cells. Bilirubinglobin does not pass the renal filter, and hence the jaundice is acholuric, as in cases due to hemolytic anemia. Red-cell destruction proceeds at a normal pace, and despite the fact that some bilirubinglobin is retained in the blood, the rates of formation and excretion of sodium bilirubinate and urobilinogen are normal or only slightly reduced<sup>24</sup>.

Regardless of the cause, jaundice of the retention type is nearly always mild. The icteric index is seldom above 30 or 40, and the quantitative van den Bergh determination reveals that most of the serum bilirubin is of the indirect variety<sup>5</sup>.

The abnormalities of pigment metabolism that may be present in either toxic or infectious hepatitis are presented in Figure 13. Sodium bilirubinate that has regurgitated around the necrotic cells and

re-entered the blood passes the renal filter, and if sufficient quantities are excreted in the urine, one or more of the various tests for bilirubinuria are positive. Since bilirubinuria often precedes clinical

jaundice, the larger portion of the serum bilirubin is of the direct variety.<sup>129</sup> The amounts of sodium bilirubinate entering the intestine from the liver also vary widely, depending on the extent of cellular

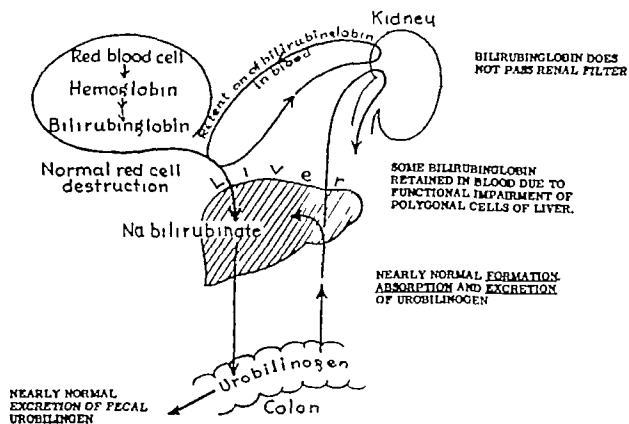


FIGURE 12. *Abnormality of Bile-Pigment Metabolism in Retention Jaundice due to Constitutional Hepatic Dysfunction.*

jaundice, the highly sensitive Harrison test is useful in screening large groups of persons who are suspected of developing hepatitis—that is, those exposed to noxious chemicals or to epidemic hepa-

necrosis and associated intrahepatic biliary obstruction and leakage from damaged cholangioles. The badly injured liver, however, cannot handle its usual large share of any urobilinogen absorbed

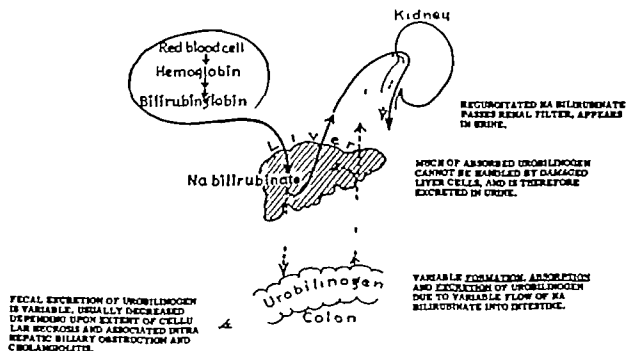


FIGURE 13. *Abnormalities of Bile Pigment Metabolism in Regurgitation Jaundice due to Hepatitis*

tus and those who have received icterogenic lots of human serum or plasma. As stated above, the quantitative van den Bergh test may give variable results in hepatitis, but at the time of maximal

from the colon, hence much of the absorbed urobilinogen is excreted in the urine.

Figure 14 serves to emphasize the fact that sodium bilirubinate that regurgitates into the blood as a

result of biliary obstruction passes the renal filter and appears in the urine, as in cases of hepatocellular necrosis. Extrahepatic block due to calculi is relatively incomplete and transient, but in about 90 per cent of cases in which malignant tumors involve the biliary tract, obstruction eventually becomes complete.<sup>15</sup> If bilirubin cannot reach the intestine, urobilinogen formation ceases, except for the few milligrams a day that are derived from the intestinal mucosa. It has been stated that increased

seen in active cases, and pigment stones, which may eventually obstruct the common duct. Jaundice in such patients may then be attributed not only to increased bilirubin production but also to biliary obstruction and to hepatocellular damage caused by both anemia and increased biliary pressure. The multiple factors operating in hepatitis have already been enumerated.

In this admittedly incomplete formulation, the pathogenesis of jaundice has been considered only

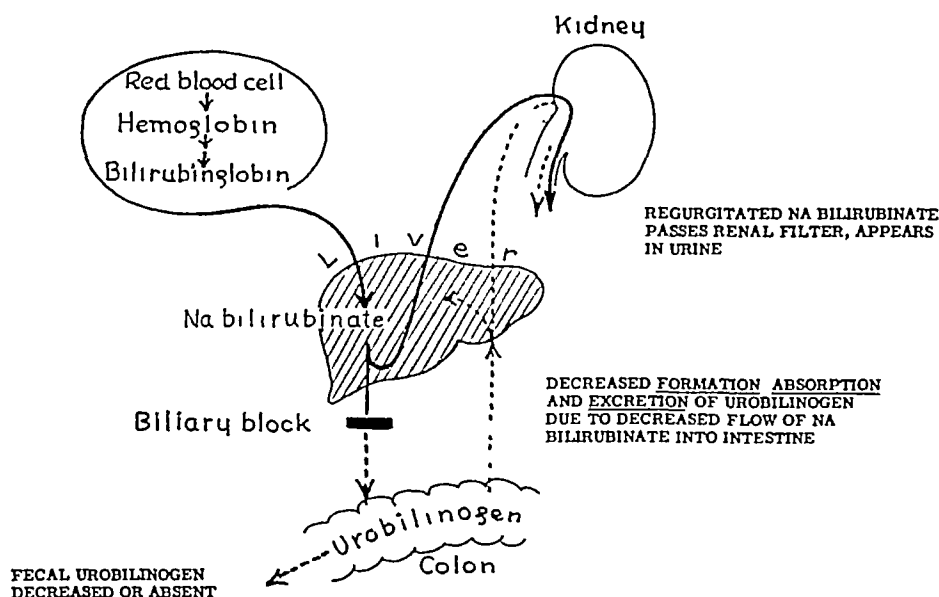


FIGURE 14 *Abnormalities of Bile-Pigment Metabolism in Regurgitation Jaundice due to Biliary Obstruction*

fecal urobilinogen excretion is the prime index of rapid erythrocyte destruction. By the same token, fecal urobilinogen excretion below 5 mg a day may be considered the most reliable indication of complete biliary obstruction.<sup>15, 147, 148</sup> When examinations of consecutive four-day fecal samples indicate the persistence of complete obstruction, it is found in the great majority of cases that the patient is suffering from cancer. If little or no urobilinogen is formed in the colon, little or none is reabsorbed and consequently urobilinogen cannot be demonstrated in the urine. In the presence of complete biliary obstruction, three factors may operate to prevent the accumulation of enormous amounts of bilirubin in the serum: urinary excretion of bilirubin, decreased bilirubin formation, and bilirubin destruction.<sup>12</sup> The last two factors require further study.

It should be emphasized that most of the various types of jaundice cannot be placed in airtight compartments, distinct unto themselves. Patients with chronic hemolytic anemia, for example, are prone to develop plugs or thrombi of inspissated bile, which block the smaller canaliculi and which may explain the occasional rise in direct serum bilirubin

as related to laboratory tests for the various hemoglobin derivatives found in blood, urine and stool. It should be stressed that hematologic studies and the results of certain liver-function tests may also be of distinct value in differential diagnosis.<sup>149-151</sup> Perhaps the most important diagnostic problem regarding jaundice is that of distinguishing between hepatitis and extrahepatic biliary obstruction—a matter that is particularly difficult when a phase of nearly complete intrahepatic obstruction is encountered during the course of hepatitis. Operation in such cases subjects the patient to an unnecessary hazard, whereas a long delay of operation in some cases of extrahepatic obstruction may also prove disastrous.<sup>152</sup> In the decision of such an issue, the history, physical findings and clinical course are most helpful. Repeated determinations of bilirubin in the blood and urine and of urobilinogen in the urine and stool are of distinct but nevertheless secondary value. Inasmuch as the pathologic processes responsible for jaundice are not static, it is essential that time relations be taken into consideration when the results of any laboratory procedures are interpreted. When decision regarding the etiology of jaundice is difficult, the clinician

obtains the best results by using and repeating at appropriate intervals a selected group of liver-function tests with which he is most familiar. Since surgery is likelier to be harmful than helpful in such cases, a period of observation to determine the course of the illness will usually prove to be time well spent.<sup>121</sup>

\* \* \*

The principal objective of this presentation has been to review current concepts of the mechanisms by which jaundice may be produced. With these mechanisms in mind, it is possible to arrive at an accurate diagnosis and to prescribe treatment in most cases on the basis of repeated bedside observations and relatively simple laboratory tests. It therefore seems inappropriate in this brief treatise to present elaborate tables of differential diagnosis and a hurried resumé of current therapeutic methods. In closing, I should like merely to state that Plato's familiar words concerning the practice of medicine seem particularly applicable to the management of the jaundiced patient: "This is an art which considers the constitution of the patient and has principles of action and reasons in each case."

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## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Annual Meeting, May 19, 1947

THE annual meeting of the Council was called to order by the president, Dr. Dwight O'Hara, on Monday, May 19, 1947, at 7:00 p. m., in the Georgian Room of the Hotel Statler, Boston.

Present were one hundred and eighty-eight councilors (Appendix No. 1).

After opening the meeting the President read the following obituary notices:

**ENOS HOTT BIGELOW**—On March 13, 1947, past president Enos Hoyt Bigelow died in Framingham where he was born ninety-one years ago. He was educated at Worcester Polytechnic Institute and Harvard Medical School, graduating from the latter and beginning practice in Framingham in 1882.

During the sixty-odd years that Dr. Bigelow practiced medicine, he had an active interest in public affairs of many sorts. In 1912 he was elected a representative in the State Legislature and in 1914 became House chairman of the Public Health Committee from which position he rendered much assistance to the Society's Committee on State and National Legislation. In 1917 Dr. Bigelow became chairman of the Society's Committee on Public Health, a position that he held for a period of years. It is of interest that these were the years during which his son George was deciding on what was to become for him a brilliant but tragic career in public health.

Dr. Bigelow served on the Board of Health and the School Committee in Framingham, he was a trustee of the Andover Newton Theological School, a member of the American Board of Foreign Missions, president of the Boston Seaman's Friend Society, the Framingham Trust Company and the Framingham Home for the Aged. He was a councillor from Middlesex South District Medical Society for many years and was president of the Massachusetts Medical Society in 1923 and 1924. Throughout his life and well into the present decade, Dr. Bigelow faithfully attended his district society meetings and until recent years he was frequently present at the meetings of the Council.

Men like Dr. Bigelow are missed, his personality was an amiable and enthusiastic influence wherever he appeared. All of us regret his passing, even as we are grateful that he was granted such a long and useful life.

**HILBERT FRANCIS DAY**—Hilbert F. Day for many years a councillor from the Middlesex South District Medical Society, passed away on May 16, 1947. He was sixty-eight years old.

Born in Roxbury, he graduated from Roxbury Latin School, of which he became a life-trustee, from Yale University and from the Harvard Medical School in 1905. He had for many years made his home in Cambridge.

Dr. Day held many prominent professional positions including those of senior surgeon at the Cambridge Hospital, surgeon-in-chief at the Boston Dispensary, professor of clinical surgery at Tufts College Medical School, consulting surgeon to many Greater Boston hospitals and president of the Middlesex South District Medical Society. He was a fellow of the American College of Surgeons and a diplomate of the American Board of Surgery.

Although in frail health during recent years, Dr. Day maintained a lively interest in a great variety of medical activities, including such causes as those of the Washing-

tonian Hospital, the Massachusetts Medical Benevolent Society, the Cambridge Tuberculosis and Health Association and the Family Society of Boston. His capacity to maintain these interests was an example of courage and firmness of purpose that evoked the admiration of his many friends. He will be long and well remembered by those with whom he worked.

**DANIEL JAMES ELLISON**—On February 15, 1947, death suddenly took Daniel J. Ellison of Lowell. Dr. Ellison was born in Rochester, New York, sixty years ago. His father before him and two of his brothers were also physicians.

He graduated from Tufts College Medical School in 1908 and subsequently served an internship at the Cambridge Hospital. He first practiced medicine in Alton, New Hampshire, moving to Lowell in 1915 at which time he was admitted to fellowship in the Massachusetts Medical Society. In Lowell, Dr. Ellison practiced continually until his death, except for a period of military service in World War I. In addition to his membership in the Society, he belonged to the American Medical Association, the American Heart Association and the New England Obstetrical Society and was a past president of the Middlesex North District Medical Society. He was a founder of the Lowell Medical Club and a staff member of the Lowell General, the St. John's and the St. Joseph's hospitals in that city. He was widely recognized and called upon in his district as a cardiologist and consultant in that field.

Dr. Ellison was a member of the Committee on Public Relations representing the Middlesex North District Medical Society and also served on several important subcommittees in connection with labor and industrial relations. He was chairman of the Subcommittee to Meet with the Medical Advisory Committee of the Industrial Accident Board. In these services Dr. Ellison could be always relied on to express himself and those he represented, incisively and with independence. He was also chairman of the Committee on Post Payment Medical Care. Altogether he was most generous of his time and energy in rendering these services to the Society.

Last February when the Council directed that its felicitations be expressed to our convalescing secretary, the mission was entrusted to Dr. Ellison, his friend and fellow townsman. Dr. Ellison responded with characteristic thoroughness and enthusiasm; it was probably his last service to the Council and one for which I fear we never thanked him for he died within the week. For his many services to the Society we are grateful.

**ARTHUR WARREN HAYES**—On March 11, 1947, Arthur Warren Hayes, of Greenfield, was stricken and within a few hours died at the Farren Memorial Hospital in Montague.

Dr. Hayes was born in Lynn in 1891 and was educated at the Lynn Classical High School. He graduated from Tufts Dental School and later from Middlesex College of Medicine and Surgery. He settled in Greenfield. For twenty-two years he served on the Greenfield Board of Health and was chairman of that board. He was associate medical examiner for the Greenfield Draft Board from 1941 on.

Dr. Hayes specialized in roentgenology; he was a member of the Radiological Society of America, a diplomate of the American Board of Radiology and a fellow of the American College of Radiology. In 1942 and 1943 he served as president of the Franklin District Medical Society and had been a member of the Council since 1943.

**MICHAEL ALOYSIUS TIGHE** — Michael A Tighe was sixty-five years old. He graduated from Boston College in 1903 and from Harvard Medical School in 1908. He had always practiced in Lowell, where he was city physician and associate medical examiner for many years. He was a member of the American Medical Association, the American College of Surgeons and the Harvard Club of Boston. He was a past president of the Middlesex North District Medical Society, and chief of the Surgical Staff at St. John's Hospital in Lowell. He became secretary of the Massachusetts Medical Society in 1941.

When the Council last met, on February 5, we joined in extending our greetings to Dr Tighe. He responded on February 10, in part as follows: "I hope to express in person at some future time my very great appreciation of the Council's action in directing you to express its high regard for me, its sorrow at my illness and its hope for my complete and rapid recovery."

This hope was not fulfilled, for after a partial return to his accustomed activities, Dr Tighe was stricken again and died within a short time on April 8. Had it been otherwise ordained Dr Tighe would, perhaps at this very moment, express to you his appreciation of our mutual regard for him. In the realm of human relations this would be nothing less than a mirror image of his regard for each one of us. I venture to say that there is among us today no one who holds the Society in greater reverence and affection than did Michael Tighe. I feel confident that he would be proud to have us stand now in tribute to all fellows of the Massachusetts Medical Society who have died during the past year, including himself, for he was one who loved his fellow men.

The Council stood in tribute to the departed members.

The President announced the following interim appointments, which were confirmed by vote of the Council:

To the Subcommittee on Mental Health, authorized by the Council on February 5, 1947:

Walter E. Barton, Norfolk  
William Malamud, Worcester  
Henry A. Tadgell, Hampshire

To the Special Advisory Committee on School Medical Services, authorized by the Council on February 5, 1947:

Stewart H. Clifford, *Chairman*, Middlesex South  
Elmer S. Bagnall, Essex North  
Florence McKay, Suffolk  
Joseph Garland, Suffolk  
James O. Walls, Worcester  
George L. Steele, Hampden  
Ernest Morris, Middlesex South

To fill the unexpired term of Secretary due to Dr Tighe's death:

Joseph Garland, Suffolk

To fill the vacancy on the Council due to the death of Dr Day:

Sylvester B. Kelley, Middlesex South

The Secretary submitted the record of the meeting of the Council of February 5, 1947, as published in the *New England Journal of Medicine*, April 17, 1947, and moved its acceptance. The motion was duly seconded. Before calling for a vote, the President read the following statement:

The Council will remember that the vote to support the Boston Medical Library was conditioned by two amendments to the effect that such support be legally appropriate to the purposes of the Society and that the Library be asked to indicate what services it might be able to provide the fellows of the Society in return for this support.

These conditions have been followed up to the point that we can announce that there are no legal impediments in the mind of our attorney, Mr. Dodge, who has provided

a statement to this effect. We have here a copy of this statement, which may be viewed by anyone interested or may be read aloud if the Council wishes.

In regard to the second condition the Trustees of the Boston Medical Library are working on a series of suggested changes in their by-laws. These changes contemplate an increase in the number of trustees from twelve to sixteen, the four new members to be appointed by the president of the Massachusetts Medical Society. It is likewise contemplated that a new class of membership in the Library be instituted, to include every fellow of the Society in good standing, who will thus become what will be known as a Massachusetts Medical Society member of the Boston Medical Library. Just what the privileges of such membership will be cannot yet be determined, but they will certainly be no less ample than those of other existing memberships at the present time. A copy of these suggested changes as they are currently conceived by the Trustees of the Library is here and is likewise open to inspection or can be read if the Council so desires.

The report was then accepted by vote of the Council.

#### REPORT OF THE TREASURER

This report (Appendix No. 2) was offered by the treasurer, Dr. Eliot Hubbard, Jr., Middlesex South, as published in the pamphlet of advance information, with one minor correction noted in the mimeographed report of the Executive Committee. Its acceptance was moved and seconded and was so ordered by vote of the Council.

#### REPORTS OF COMMITTEES

*Executive Committee* — Dr. Joseph Garland, Suffolk, *Secretary*

The Secretary submitted the report of the meeting of April 23, 1947, as circulated in mimeographed form (Appendix No. 3), and moved its acceptance. The motion was seconded, and it was so ordered by vote of the Council.

*Auditing Committee* — Dr. Howard B. Jackson, Norfolk, *Chairman*, and Dr. Frank T. Downey, Middlesex South

The chairman being absent, this report, which is as follows, was presented by the President:

The Auditing Committee appointed the firm of Hartshorn and Walter, accountants and auditors, to audit the books and accounts of the Massachusetts Medical Society. This audit and account are hereby approved by us.

The analysis of the revenues and expenses of the Society and the balance sheet of the condition of the funds of the Society have been inspected and approved by us.

Its acceptance was moved and seconded, and it was so ordered by vote of the Council.

*Committee on Arrangements* — Dr. Sidney C. Wiggan, Suffolk, *Chairman*

The following report was presented by the chairman:

The Committee on Arrangements wishes to report on the final program for the annual meeting — May 20, 21 and 22.

We believe that an exceptionally interesting program has been arranged for the general practitioner and that the section luncheon programs will be of unusual interest and value to the specialty fields.

We wish to call your attention to the technical exhibits in the ballroom and foyer. These cover the development of many new medical supplies and equipment and much can

be gained from them. We wish to encourage the co-operation of every member of the Society in visiting these booths during the meeting, as it is the income from their rental that makes meetings such as this possible.

The medical exhibits have not come up to our expectations and we would suggest another year that special effort be made to stimulate the members of the Society and especially the hospitals to develop exhibits of their most interesting medical developments that would be of help to the general practitioner of Massachusetts.

This year the members of the Massachusetts Physicians' Art Association formerly the Boston Physicians' Art Society are having their first exhibit in conjunction with the annual meeting at the Hotel Statler. This is the first exhibit of its kind since 1938. It is being organized by Dr James C. Janney, vice-president of the Association. This should prove of great interest to the members of the Massachusetts Medical Society and their wives.

Its acceptance was moved by the chairman, was seconded and was so ordered by vote of the Council

*Committee on Ethics and Discipline*—Dr Ralph R. Stratton, Middlesex East, Chairman

The following report was presented by the chairman

During the past year between fifty and sixty complaints and inquiries concerning ethical procedures have been received by the committee, necessitating much investigation and six all-day and two special sessions of the committee.

There have been rather more inquiries as to ethics and procedures this year than usual coming from all parts of the Commonwealth, indicating a more healthy ethical sense on the part of the members at large.

Several fellows have been deprived of membership in the Society because of the decisions of the State Board of Registration of Medicine and Chapter 1 Section 9, of our by-laws. This separation has been without any loss to the efficiency and dignity of the Massachusetts Medical Society.

Numerous run-of-the-mill complaints have been received and investigated. Following conversations with the chairman several of these complaints have been withdrawn. The others have been investigated and viewed by the committee and settled on their merits without any loss of prestige to the fellow and with greater or less satisfaction to the complainant.

A number of complaints against fellows of more serious nature have been received and investigated. These included such complaints as unethical advertising, serious neglect in the care of a patient by the physician and over charging for value received. All these cases have been investigated, reviewed and settled by the committee. Space does not allow further elaboration.

Two cases however, must be discussed. The first is a complaint of fellow against fellow for definite violation of the Code of Ethics in his treatment of the other fellow's rights. The fellow was found guilty of deliberate violation of the code, was reprimanded by the committee, ordered to apologize to the offended fellow and referred to the President for censure. A copy of an apology was received by the committee, the President notified us that the case had been applied and the case was considered closed.

In the second case, a physician complained that a fellow used language at a public hearing derogatory to his reputation and standing as a physician, which language unfortunately was published in the newspapers. In conversation with the chairman the fellow offered to apologize to the offended physician, the committee accepted this offer and requested the fellow to send an apology to the offended physician and forward a copy to the committee. Upon receipt of this apology the matter was considered closed.

The committee was unhappy and somewhat concerned at the receipt of these two apologies, for while they were apologies they were couched in such language that the committee felt that in neither case did the fellow show any penitence for his deed. The committee will watch with interest the future ethical observances of these two fellows, that of the first because during his interrogations he showed

a definite ignorance of what constitutes ethical conduct and that of the second because of his apparent indifference to the code by reason that this is the second time within a comparatively few months that he has been obliged to apologize to a fellow for unethical acts.

In this connection the Committee on Ethics and Discipline calls attention to the following circular, which has been prepared under the auspices of the supervising censors

#### Attention of the Candidate

When you are admitted to membership in the Massachusetts Medical Society, you will be supplied with its Code of Ethics and with the Principles of Medical Ethics of the American Medical Association to all of which you shall be required to subscribe.

You are urged to study this code and these principles to the end that you may conduct your professional life in a manner befitting an honorable physician.

So that you may have some preliminary knowledge in this subject the supervising censors submit to you at this time a brief summary of these requirements.

You shall be required to regard the welfare of your patients as taking precedence over your own comfort or your financial or other material gain.

They shall receive at your hands thorough examination and sympathetic treatment of their ills. You shall make due allowance for their peculiarities.

The seal of secrecy shall govern your relations with them to be broken only in accordance with the civil law of the Commonwealth or on the direct order of the civil authority.

Their ailments, therefore, shall not be the subject of gossip.

You shall encourage sound medical learning as the *sine qua non* of good medical care and as a corollary of this you shall distinguish between legitimate medicine and quackery and have no part or interest in the development or distribution of secret remedies.

You shall call attention to your professional qualifications only by the performance of work well done.

You shall not seek professional advantage at the expense of a fellow practitioner. Honor and courtesy shall govern your relations with him.

You shall not by actual act or by innuendo seek to divert another's patient to yourself.

The practice of fee splitting is forbidden in any guise whatsoever.

It will be your obligation to contribute your time and energy to the end that the Massachusetts Medical Society may continue to represent the ideals of the medical profession.

Inquiry has revealed the fact that a supply of these circulars has been distributed to the district secretaries by the Secretary with the direction that each applicant be handed a copy with his application, that he be examined on its contents and that the censors determine his fitness for membership to a large extent by the answers that he gives.

The Committee on Ethics and Discipline recommends that the Council by its vote give further emphasis to the importance of this procedure and that the Secretary be instructed to so notify the district secretaries.

The acceptance of the report was moved by the chairman. The motion was seconded and it was so ordered by vote of the Council.

Dr Stratton then went on to call to the attention of the Council the recommendation that the Committee on Ethics and Discipline was making concerning the notice that had been drawn up by the supervising censors and was presented to each candidate for admission to the Society. He said that it was

the belief of the committee that this notice should be given the approval of the Council, because after its perusal no candidate could come into the Society without a working knowledge of the *Code of Ethics* of the Society and *Principles of Medical Ethics* of the American Medical Association. It was brought out by Dr Stratton that in the last few years a number of cases have come before the committee in which the offending fellow had apparently no acquaintance with the *Code of Ethics* and knew nothing about ethical procedure with regard to his relations with his fellows. This synopsis of the *Code of Ethics* constitutes part of the material on which the candidate is examined by the censors of his district.

Dr Stratton then read the recommendation of the committee and moved its adoption, to give emphasis to the *Code of Ethics* of the Society. The motion was seconded.

Dr Carl Bearse, Norfolk, offered as an amendment to the motion that a copy of the notice also be sent to every member of the Society with the next general mailing. After some discussion the amendment was adopted.

Dr Stratton moved the adoption of the recommendation as amended. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Public Relations*—Dr Albert A Hornor, Suffolk, *Secretary*

This report, which follows, was presented by the President. It is divided into three items, which were recommended for acceptance by the Executive Committee.

1 The Subcommittee on Insurance Relations, which was appointed in accordance with the direction of the meeting of the Council in October, 1946, made the following report to the Committee on Public Relations:

The committee is aware of the desire and interest of the American Medical Association in the development of plans for prepayment medical care throughout the United States. Several years ago the Massachusetts Medical Society took steps aimed at the provision of prepayment medical care for the people of Massachusetts and has placed in operation a plan to effect this idea. This program has now been subscribed to by over half a million people in this state and is rapidly increasing in its acceptance by the public.

This committee feels that any plan aimed at extending the opportunity for prepayment medical benefits to the residents of this State is commendable.

HAROLD G GIDDINGS  
A J A CAMPBELL  
NORMAN A WELCH  
DONALD MUNRO, *Chairman*

This report was accepted and approved by unanimous vote of the Committee on Public Relations.

The Committee on Public Relations recommends that this report be accepted and approved by the Council and that the subcommittee be discharged.

2 In accordance with the instructions of the Council at its February meeting in 1946, the Committee on Public Relations has studied the question of establishment of a women's auxiliary to the Massachusetts Medical Society. This has been reported on three times by the subcommittee, consisting of Dr Milton J Quinn, chairman, Dr Harold R Kurth and Dr Albert A Hornor.

At the November meeting of the Committee on Public Relations each district society representative on the Committee on Public Relations was directed to bring the opinion of his respective society to the next meeting of the Committee on Public Relations.

At the meeting March 19, 1947, reports from eleven district societies were recorded, as follows: five in favor, four opposed and two no action. The Committee on Public Relations recommends:

That the Council extend to each district the privilege of forming, at the district's pleasure, a women's auxiliary. That the Council authorize the Committee on Public Relations to aid in the organization of these said units.

3 As a report of progress the Committee on Public Relations submits the following items:

The establishment of a Speaker's Bureau was discussed. Dr John Conlin, who was present as a guest, told us that when he began to work he wanted to be able to come to the committee for help and guidance. The problem was discussed freely by all present and it was decided that each member of the Committee on Public Relations would come to the next meeting prepared to discuss this question with Dr Conlin.

Dr Harold R Kurth, representative of the Essex North District Medical Society, made the following report:

At a meeting of the Essex North District Medical Society there was considerable discussion between the members of the society and Mr R F Cahalane, director of the Blue Cross, with reference to the payment of anesthetist's fees by the Blue Cross. Under the present ruling the Blue Cross pays anesthetist's fees only to those individuals who are regularly employed as anesthetists by the hospitals.

It is the feeling of the members of this district that this present arrangement prevents many private physicians who give anesthesia to Blue Cross patients from being paid an anesthetist's fee, simply because they are not regularly employed as such by the hospital, whereas the regularly employed anesthetist of the hospital is paid. In some cases these regularly employed anesthetists are merely nurses, trained in anesthesia.

Therefore, the Essex North District Medical Society presents the following resolution to the Massachusetts Medical Society, namely:

That the whole question of the payment of anesthetist's fees by the Blue Cross be reconsidered.

This report brought general discussion of the subject of the relation of the members of the Massachusetts Medical Society to the Blue Cross and the Blue Shield. It was moved by Dr Charles D McCann, Plymouth, and seconded by Dr Kurth that the chair appoint a committee of three to investigate this problem and report at the next meeting of the Committee on Public Relations, if necessary having a special meeting to discuss these problems. The committee was instructed to get from each member of the Committee on Public Relations his ideas of the problems presented and what should be done about them.

This motion was passed unanimously and the chair appointed, as members of that committee, Dr Kurth, Dr McCann and Dr Albert A Hornor.

The first item comprises the report of the Subcommittee on Insurance Relations and contains the recommendation, "Any plan aimed at extending the opportunity for prepayment medical benefits to the residents of this state is commendable."

Dr Bagnall, Essex North, in discussion, questioned the wisdom of such an inclusive endorsement of prepayment medical benefits and moved that the report be returned to the subcommittee for further study. This motion was seconded.

Considerable discussion was participated in by Drs William E Browne, Suffolk, Donald Munro, Suffolk, Frank R Ober, Suffolk, and Peirce H Leavitt, Plymouth Dr Leavitt offered as an amendment to Dr Bagnall's motion that "any plan aimed at extending the opportunity for prepayment medical benefits to the residents of this state may be commendable" This amendment was seconded

Dr Sosman, Suffolk, offered a further amendment to make the last sentence of the report read

*This committee feels that any plan which conforms to the basic principles adopted by the Society in regard to medical-service plans and which is aimed at extending the opportunity for prepayment medical benefits to the residents of this state is commendable.*

This amendment was seconded After further discussion, the question was put to vote and Dr Leavitt's amendment was defeated Dr Sosman's amendment was then put to vote and adopted by the Council, after which the recommendation as a whole was adopted

The second item in the report of the Committee on Public Relations concerns the establishment of a women's auxiliary within the Society The committee report recommended action by the Council to permit the establishment of women's auxiliaries within the district societies and to authorize the Committee on Public Relations to aid in the organization of these units

Dr Milton J Quinn, Middlesex East, spoke in favor of the recommendation so convincingly that Dr Bearse, Norfolk, offered the following amendment, "In addition to the districts being privileged to form these women's auxiliaries, there also be established a women's auxiliary to the Massachusetts Medical Society" This motion was seconded by Dr Quinn and was so ordered by the Council

The main recommendation of the committee, to permit the establishment of women's auxiliaries within the districts, was then put to vote and was so ordered by the Council

The remainder of the report of the Committee on Public Relations gave information on two points, first, the establishment of a speakers' bureau, and second, a discussion that had taken place within the Essex North District with reference to the payment of anesthetist's fees by the Blue Cross

President O'Hara, in mentioning this part of the report, made the Council aware of action that would be asked of the Council on this subject later in the meeting

The entire report of the Committee on Public Relations was then accepted by the Council

*Committee on Legislation* — Dr George R Dunlop, Worcester, Dr David L. Belding, Norfolk South, Co-chairmen

The following report was offered by Dr Dunlop

Since the opening of the 1947 session of the Massachusetts Legislature in January there has been one meeting of the committee and three meetings of the executive subcommittee, at which a total of thirty nine bills has been considered It has been voted to favor seven, oppose thirteen, and take no action on nineteen of these bills. The 'no action' bills have been chiefly concerned with general sanitation departmental activities and economic problems not intimately connected with the practice of medicine. Favorable action has been taken on five bills of the Massachusetts Department of Public Health, the one concerning blood tests in illegitimacy (H. 145) and that covering tuberculosis in school teachers (H. 705)

The bills opposed by your committee are those that lower medical standards and limit medical practice and research. The important chiropractic bill (S. 151) was given leave to withdraw by the Legislative Committee on Public Health at the request of the petitioners S. 26 and H. 974 for opening hospitals to all physicians have been successfully opposed H. 1211 which would lower standards for licensed attendants has been withdrawn. H. 706 relating to the College of Physicians and Surgeons H. 633 regarding the unionization of hospital employees H. 541 revoking certain powers of medical examiners and three minor bills have been opposed. The antivivisection bills (S. 47 H. 126 and H. 1361) were reported unfavorably by the Legislative Committee on Legal Affairs. Opposition was efficiently handled by a special Committee on Antivivisection with members from the three Massachusetts medical schools the Massachusetts Medical Society and the Associated Catholic Hospitals.

At the February meeting the Council voted that the Committee on Legislation aid in expediting Dr Gettings' program for (1) raising the salary level of the professional personnel engaged in public health on a state or local basis, (2) instituting a sanitary code (3) providing subsidization of local health departments, and (4) promoting town unions of adequate size to support a modern public and school health program. The last two topics are not under consideration by the Legislature this year. Your committee has favored the sanitary-code bill (H. 78) It has presented to Governor Bradford the recommendation of the Massachusetts Medical Society that the professional salaries in the Department of Public Health and the Department of Mental Health be placed at levels that will allow Massachusetts to compete with outside agencies. It has also obtained the co-operation of the *New England Journal of Medicine* in publishing an editorial on this subject.

On March 27, Dr Bagnall, chairman of the Subcommittee on National Legislation and the official representative of the Council, appeared before the Senate Committee on Expenditures in the Executive Departments at Washington and recorded the opposition of the Society to S. 140 and S. 712, bills creating a tripartite department of health, education and security. The Subcommittee on National Legislation finds that the Taft Bill (S. 345) in general conforms to the principles established by the Massachusetts Medical Society but that certain minor changes are necessary to make it acceptable. The Committee on Legislation will present the views of the Society before the appropriate committee when hearings on the bill are held at Washington

The announcement by Dr Dunlop that all thirteen bills opposed by the committee were rejected by the Legislature was greeted with applause

Of the seven bills favored, one was enacted and among the four rejected was H. 78, on the sanitary code, which the Council had favored at the February meeting. Two bills, that for licensing of hospitals and the bill requiring x-ray examination of chests of schoolteachers, were still in committee. The report was accepted by the Council

*Committee on Medical Defense* — Dr Arthur W. Allen, Suffolk, *Chairman*

The following report was offered by Dr Allen

We now have seven cases pending. During the past year, we have disposed of three suits — one of these was dismissed for lack of prosecution and the other two were settled out of court.

Five new cases have been added during the past year. This is a definite increase over recent years. We believe that some of these will not be brought to trial for lack of evidence. One or two of them may prove to be quite troublesome.

There has been increasing difficulty in obtaining satisfactory expert witnesses for the defense of our fellows. Councilors are urged to assist our attorneys in these matters whenever possible. Many members of the Society have given freely of their time and advice when called upon.

The charges for legal services for the past year amounted to \$1,167.75. This represents the entire expenditure of this committee.

Dr Allen moved the acceptance of the report. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Publications* — Dr Richard M. Smith, Suffolk, *Chairman*

This report (Appendix No. 4) was submitted as published in the circular of advance information. Dr Smith moved its acceptance. The motion was seconded, and it was so ordered by vote of the Council.

*Committee on Veterans' Affairs* — Dr G. Philip Grabfield, Suffolk, *Chairman*

This report is as follows:

The committee has held no formal meetings since our last report because no questions have been referred to it and none of the members had any suggestions to make on which action was necessary. It appears that most of the immediate veteran's problems have been considered and solved in so far as it was possible for the Society to do so. The committee is unanimous in feeling that any committee that has no work to do should be dissolved and yet it is hesitant about a firm recommendation to terminate its existence due to the doubt that exists as to the possibility of further veterans' problems being brought before the Society.

It is therefore recommended that the Veterans' Committee remain in existence until after the annual meeting in 1947 in order to deal with any veterans' problems that may come up at that time and that if no such problems appear at the annual meeting the committee be discharged.

The President, in commenting on this report, called the attention of the Council to the action of the Executive Committee regarding it. The Executive Committee viewed with some concern the continuing complications in the present relations between the Society and the Veterans Administration and on that account recommended the omission of the part of the report calling for the discharge of the committee after the annual meeting. This recommendation was accepted, and the report as thus amended was accepted by vote of the Council.

*Committee to Confer with the Massachusetts Farm Bureau Federation* — Dr Joseph C. Merriam, Middlesex South, *Chairman*

The following report was offered by Dr Merriam:

This report is informational. Through the chairman of this committee the headquarters of the Massachusetts Farm Bureau was notified that the committee had been appointed and was ready to meet with them to discuss any medical problems they may have and to help them in any way within its power.

The chairman was assured by the Farm Bureau that they had no medical problems but should any arise the committee would be notified.

Dr Merriam moved the acceptance of this report. The motion was seconded, and it was so ordered by vote of the Council.

*Committee to Survey Salaries* — Dr Charles J. Kickham, Norfolk, *Chairman*

The following report was offered by Dr Kickham:

This committee, which was ordered by the Council to consider a retirement plan, has met and after consideration has found that the problem is very complex. We have to give consideration to the age limits, the cost, the amount of compensation to be received at retirement and many other details.

The committee unanimously agreed that considerable time would be necessary before any decision could be made and that we should have one or more plans submitted to us by competent insurance companies to guide us in our study. It was felt that this would take months and consequently at this time we simply submit a report of progress.

Dr Kickham moved the acceptance of this report. The motion was seconded, and it was so ordered by vote of the Council.

*Committee to Aid the Regional OPA* — Dr Joseph Garland, Suffolk, *Chairman*

The following report was offered by Dr Garland:

This committee was appointed at the annual meeting of the Society in 1943 to advise the Regional Office of Price Administration on the medical aspects of food rationing. During the war years and so long as active rationing continued, its duties were considerable and their performance of some possible value to the war effort. For over a year the occasional rationing problems have been confined to the dispensing of sugar.

As of June 30, 1947, the Office of Price Administration goes out of existence and your committee, desiring not to outlive its usefulness by too long, requests that it also be discharged.

Dr Garland moved the acceptance of this final report and the discharge of the committee. The motion was seconded, and it was so ordered by vote of the Council.

*Report of the Committee to Meet with General Hawley* — Dr Humphrey L. McCarthy, Norfolk, *Chairman*

This report (Appendix No. 5) was submitted as published in the circular of advance information. Dr McCarthy, in presenting the report, explained the difficulties that had been encountered in attempting to co-operate with the Veterans Administration through a Blue Shield contract. These difficulties were based largely on the opposition of the American Legion and the Veterans of Foreign Wars to two bills filed by Blue Shield and Blue Cross which would allow these organizations to sign con-

tracts with a federal or local agency. As stated in the report of the Executive Committee (Appendix No. 3) these bills were reported three times unfavorably by the Insurance Committee of the Legislature, making it impossible to continue with the Blue Shield contract. Dr. McCarthy accordingly recommended a new type of program in which the Society would deal directly with the Veterans Administration under a gentleman's agreement, similar to the so-called "Kansas Plan."

To facilitate this change in policy the Executive Committee recommended three actions by the Council:

(1) To remove from the table, where it was placed by vote of the Council on October 2, 1946, the recommendation of the Executive Committee that the vote of the Council of April 10, 1946, in special meeting be rescinded. (This vote adopted the plan of a contractual arrangement between the Veterans Administration and the Blue Cross-Blue Shield whereby the hospital expenses of veterans in civilian hospitals would be met by the Blue Cross as agent and whereby the costs of professional services of civilian physicians caring for veterans under the fee schedule would be met by the Blue Shield as agent.)

This was moved by Dr. McCarthy, the motion was seconded, and it was so ordered by vote of the Council.

(2) To rescind the vote of April 10, 1946.

This was moved by Dr. McCarthy, the motion was seconded, and it was so ordered by vote of the Council.

(3) To refer the whole matter back to the Committee to Meet with General Hawley for further negotiations along the lines of a gentlemen's agreement and report to the Council.

This was moved by Dr. McCarthy, the motion was seconded, and it was so ordered by vote of the Council.

Dr. McCarthy then moved the acceptance of the entire report. The motion was seconded, and it was so ordered by vote of the Council.

On motion from the floor, unanimously carried by the Council, Dr. McCarthy was given a vote of thanks for "the enormous amount of work that he has put into this program, is putting in and will probably continue to put in."

*Committee on Postgraduate Instruction*—Dr. W. Richard Ohler, Norfolk, Chairman.

This report (Appendix No. 6) was submitted as published in the circular of advance information. In presenting it, Dr. Ohler pointed out that it also included a report of the Bureau of Clinical Information.

The report contained one recommendation, that the program as carried on last year, which includes the Sanders Theater Exercises, be continued another year.

President O'Hara, in commenting on this recommendation, noted that the instruction sponsored by the committee, figured on the basis of the usual col-

legiate semester hours, amounted to a complete college course given for thirty or forty men, all in one year.

The recommendation was carried, after which the acceptance of the report as a whole was moved by Dr. Ohler. The motion was seconded, and it was so ordered by vote of the Council. Dr. O'Hara's expression of the Council's gratitude to Dr. Ohler was greeted with applause.

*Joint Committee on Rehabilitation and Industrial Health*—Drs. Daniel Lynch, Norfolk, and Joseph H. Shortell, Suffolk, Chairmen.

The following report was offered by Dr. Lynch:

On April 2, 1947, there was a joint meeting of the Committees of Industrial Health and Rehabilitation. Present for the Committee of Industrial Health were Drs. Daniel Lynch, chairman, Harold R. Kurth, Louis Daniels, and Thomas Shipman. Present for the Committee on Rehabilitation were Drs. Joseph Shortell, chairman, Ralph Chambers, James Regan, Arthur Watkins, and members *ex officio*: Drs. Dwight O'Hara and Edward P. Bagg. As guest advisers were Drs. Henry Marble, Alexander Altken, director of the Liberty Mutual Rehabilitation Clinic, Mrs. Emma Tossant, member of the Industrial Accident Board and Mr. Herbert Dallas, Division of Vocational Rehabilitation.

The whole field of rehabilitation was discussed and particularly Dr. Augustus Thorndike's request as to whether there is need for a community rehabilitation center and service in Boston. Dr. Thorndike was present and fully explained the proposed establishment of a rehabilitation clinic.

It was resolved that the joint Committee of Rehabilitation and Industrial Health agrees that there is a definite need for the establishment of a community rehabilitation center and service in Boston in accordance with the Report of the Baruch Committee on Physical Medicine, but that it should be established maintained and controlled locally and not nationally, and that such a project is advisable.

Dr. Lynch moved the acceptance of the report.

President O'Hara then asked Dr. Augustus Thorndike, Suffolk, to discuss the report, since the consideration of a community rehabilitation center had resulted from a resolution presented by him at the February meeting of the Council.

Dr. Thorndike, in discussion, explained that what is planned by the Baruch Committee on Physical Medicine would not proceed without the approval of the Society, and would be a nonprofit organization with outpatient and consultation service for the physically handicapped, where doctors and hospitals could refer their patients for late convalescent care. Such a clinic would be available to all economic classes. At present, to the best of Dr. Thorndike's knowledge, the Liberty Mutual Rehabilitation Clinic is the only medically supervised center in New England.

Dr. Donald Munro, Suffolk, in emphasizing the point that the economic status of the patient was not a matter of consideration, explained that only through such a clinic could certain types of patient, such as those with paralysis from spinal injuries, receive proper care.



Drs Lynch and Arthur L. Watkins, Middlesex South, spoke further in support of the establishment of such a center.

The motion to accept the report was seconded, and it was so ordered by vote of the Council.

*Committee on Physical Medicine*—Dr Arthur L. Watkins, Middlesex South, *Chairman*

The following report was offered by Dr. Watkins:

This committee has had no new work assigned to it, but would like to make an informational report on activities in physical medicine in this area. The Veterans Administration has established a far-reaching plan for medical rehabilitation in all its hospitals. This includes physical and occupational therapy, physical rehabilitation and shop and educational retraining, all under the direction of a specialist in physical medicine termed a physiatrist. This program aims to carry the patient through the convalescent or third stage of medical care and guide him toward suitable employment.

The plan for a New England rehabilitation center for civilian casualties of disease and injury recognizes a similar need for more complete medical care during convalescence, particularly employing physical medicine, including evaluation for employment capabilities.

The recent literature in physical medicine has again been reviewed and will appear in the *Journal* as a progress report entitled "Recent Trends in Physical Medicine."

Dr. Watkins moved the acceptance of the report. The motion was seconded, and it was so ordered by vote of the Council.

Dr. Paul R. Withington, Norfolk, having raised a question as to the formation of women's auxiliaries, Dr. O'Hara put to a vote the question of returning to the report of the Committee on Public Relations for further discussion. This was not carried.

*Committee on Nominations*—Dr. Ralph R. Stratton, Middlesex East, *Chairman*

In the absence of Dr. Stratton, Dr. Allen G. Rice, Hampden, presented the following supplementary report of the committee:

A special meeting of the nominating councilors, called by President Dwight O'Hara, was held Wednesday, April 30, 1947, at 4:00 p.m. in the Prince Room, 8 Fenway, Boston.

The untimely death of the Secretary, Dr. Michael A. Tighe, and the withdrawal by Dr. Edmond F. Cody of his nomination for vice-president left these positions unfilled. At this special meeting the nominating councilors nominated for secretary Dr. Joseph Garland, Suffolk, and for vice-president Dr. Charles J. Kickham, Norfolk.

The slate of the nominating councilors is therefore amended to read as follows:

President-elect	Daniel B. Reardon
Vice-president	Charles J. Kickham
Secretary	Joseph Garland
Treasurer	Eliot Hubbard, Jr.
Assistant treasurer	Norman A. Welch
Orator	Allen S. Johnson

The President asked for nominations from the floor. There being none, Dr. Rice moved that the Secretary be instructed to cast one ballot for the list of officers as submitted by the Committee on Nominations. This motion was seconded, and it was so ordered by vote of the Council.

This vote having been cast, the President announced that the list of officers as read had been elected.

President O'Hara then introduced Dr. Edward P. Bagg, president of the Society for the 1947-1948 term of office, as follows:

Dr. Bagg, last year Dr. Fitz presented me with ten volumes of the proceedings of the Society, each one autographed by the president of that year, for ready reference of the president, and you will find those, sir, in the presidential desk at 8 Fenway. You will also find there an eleventh volume, which is the proceedings of the Society for 1946 and inscribed by Dr. Fitz, to carry on the tradition that he commenced.

I have at this time the honor to present to you, which Dr. Fitz presented to me, the presidential copy of *Robert's Rules of Order* and the keys to the Society. They will let you in at 8 Fenway, where you may wander at will. We welcome you into your presidency, sir.

Dr. Bagg made the following reply:

Dr. O'Hara, I thank you for these donations, which are much needed. I don't know about the keys, but *Robert's Rules* will have to be my constant companion, I can see. If we can only emulate the example that has been set us this year with a modicum of success, I shall be satisfied. That is not a mere chance remark, either. As you know, Dr. O'Hara has put a great deal of time and thought into these meetings, and one of the reasons they have moved along so successfully is that he knew the agenda and he knew what the Executive Committee had discussed.

It has been a privilege this past year to sit in with these committees and see them function and to learn the personalities involved, and I feel better prepared tonight than I did a year ago. But I know I shall need all your assistance.

We shall miss Dr. Tighe greatly. As Dr. O'Hara has told you, there are very few members who have had such a warm interest in the affairs of the Society.

I think this might be the proper occasion to tell you about a rather dramatic episode. Dr. O'Hara and I had talked things over after Dr. Tighe's first attack, and we had decided that it was too much for him to undertake the secretaryship and private practice. So I wrote him a letter asking him if he would care to have me bring in a resolution suggesting that the secretaryship should be made full time, because we felt that he should not jeopardize his health with general practice. I wish you could have seen the expression on his face as he sat there. He was delighted beyond words and overcome with the suggestion and said he would go home and think it over. I had a letter from him several days later stating that after prolonged thought, for it was not an easy decision, he had decided to accept if the Society felt that they wanted him for full time service. And then of course he ended, "And I am delighted to say that I am sound again and ready for work." But five days later he was called to other fields. It is at least, however, a great satisfaction to me to think that he had that one joyous experience. The question whether the position should be made full time can wait and need not be discussed this evening, but at least I do not regret having written that letter. We shall go into that some time at length.

But once more, gentlemen, let me thank you for the honor. I will do my best to live up to the privileges as well as the responsibilities.

Dr. Daniel B. Reardon, Norfolk South, president-elect, was then escorted to the platform and introduced to the Council. Dr. Reardon addressed the Council as follows:

I wish to thank each and every one of you individually for having elected me to the office of president-elect. I shall now take Dr. Bagg's position as a sitter for the next year, and I expect to gain considerable profit in occupying that position.

I am thoroughly familiar with many of the committees because I have served on a good many of them so some of their work will not be new to me. I accept this offer with a keen appreciation of the responsibility which it holds. I do it with a sense of deep humility. My earnest endeavor shall be to serve you and to serve the Society as well as possible and at all times to maintain the dignity and honor of that office. Thank you

After the introduction of the remainder of the slate of officers elected, the President called for new business to come before the Council, as the president-elect was not at the moment prepared to submit his list of committee appointments

### NEW BUSINESS

Dr Merrill C Sosman, Suffolk, rose to present a joint resolution by the roentgenologists, pathologists and anesthesiologists of Massachusetts. As a preliminary explanation he reminded the Council that the Blue Cross had just sold a comprehensive, all-inclusive contract at a per-diem rate, and he stated that the three groups mentioned had objected to it on three principles first, that it includes medical services as hospital care, second, that it puts the hospital in the bad situation of "holding the bag" with an unpredictable amount of insurance, as Blue Cross has guaranteed to cover all x-ray charges regardless of cost, but pays for them only on a per-diem rate, and third, that it puts control of the professional services more into lay hands than it has been before

Dr Sosman then presented the following resolutions

WHEREAS, Massachusetts Hospital Service agreements which affect the professional status of pathologists, radiologists, and anesthesiologists have been offered to the public and hospitals without consultation with representatives of the organizations of these specialists in Massachusetts, and

WHEREAS, Radiology (sometimes referred to as roentgenology or x-ray examination, diagnosis or treatment) pathology (sometimes referred to as laboratory examination or diagnosis) and anesthesiology constitute the practice of medicine and are medical services and

WHEREAS, The House of Delegates of the American Medical Association on June 8 1943, recommended

That the House emphatically reiterate that it disapproves the injecting of a third party into the personal relationship of the patient and the physician and that hospitals should not be permitted to practice medicine.

That the practice of radiology pathology and anesthesiology is the practice of medicine just as much as is the practice of surgery or internal medicine, and that it is only a short step from including the first three in a medical service plan to including the whole field of medicine in such a plan, and

WHEREAS, We are heartily in accord with the basic principle of insurance against the cost of sickness and hospitalization by voluntary prepaid plans in accordance with the principles adopted by the Massachusetts Medical Society, and

WHEREAS, The proposed over-all comprehensive Massachusetts Hospital Service agreement on a per diem basis of compensation fails to distinguish between hospital services and professional medical services, such as pathology x ray and anesthesia and

WHEREAS, The proposed Massachusetts Hospital Service agreement on a per diem basis submerges completely the

professional standing of the services of the pathologist, radiologist and anesthesiologist and relegates them to a hospital service similar to room board and drugs, and

WHEREAS, The introduction of the proposed per diem plan which includes professional services will undoubtedly lead to an unpredictable increased volume of work, especially in radiology and could result in control of professional services by hospital administrators, thus lowering the quality of the work with the inevitable danger to the public welfare and

WHEREAS, At the present time there is a shortage of well trained pathologists radiologists and anesthesiologists in this country and whereas an important factor in this shortage is the tendency for hospitals to minimize the professional standing of these specialists and thus not attract the best class of physicians to these specialties and furthermore a per diem basis of payment will certainly increase this trend so that these specialties may lose their standing as professional specialties therefore be it

RESOLVED, That the New England Pathological Society, the New England Roentgen Ray Society the Section of Radiology of the Massachusetts Medical Society the New England Society of Anesthesiologists and the Section of Anesthesiology of the Massachusetts Medical Society oppose any arrangement by any hospital with the Massachusetts Hospital Service that will allow this organization to guide or determine professional services and furthermore be it

RESOLVED, That the New England Pathological Society the New England Roentgen Ray Society the Section of Radiology of the Massachusetts Medical Society the New England Society of Anesthesiologists and the Section of Anesthesiology of the Massachusetts Medical Society oppose the principle of the over all comprehensive Massachusetts Hospital Service Agreement on a per diem basis of compensation because it fails to distinguish between hospital services and professional medical services such as pathology, x ray, and anesthesia and furthermore be it

RESOLVED, That they recommend that charges for all professional services performed by physicians should be specifically excluded from all hospital service plans

The New England Pathological Society the New England Roentgen Ray Society the Section of Radiology of the Massachusetts Medical Society, the New England Society of Anesthesiologists, and the Section of Anesthesiology of the Massachusetts Medical Society recommend

That the logical organization to write insurance against professional charges is the Blue Shield rather than the Blue Cross and that these two organizations attempt to work out a method of collaboration to cover these items.

That since contracts including professional services have been sold, it is proposed as an interim arrangement that charges for these professional services be billed directly by the hospital to Blue Cross and per diem rates be appropriately reduced by quota to compensate for this amount.

Since this contract was to go into effect on June 1, Dr Sosman moved that Rule 1 of the Council, requiring all new business offered at Council meetings to be referred to a committee, be suspended, as provided for by Rule 3. The motion was seconded.

President O'Hara referred the resolution to the Committee on Public Relations, because that committee already had a subcommittee working on the anesthesiologists' aspect of the problem. He then called for discussion of the motion to suspend the Council rule. After considerable discussion by Drs Bagnall, Sosman and Schadt, the motion was passed.

Dr Sosman then moved that the Council approve the resolutions presented by the New England Pathological Society, the New England Roentgenological Society, the Section of Radiology of the Massachusetts Medical Society, the Section of

Roentgenology of the Massachusetts Medical Society, the New England Society of Anesthetists, and the Section of Anesthesiology of the Massachusetts Medical Society. The motion was seconded, and the Council voted to approve the resolutions.

Dr Bagnall then moved that this whole matter be re-referred to a subcommittee of the Committee on Public Relations to be appointed by the President for a thorough study and report to the Council. The motion was put to vote and failed to be approved by the Council.

Dr Charles J Kickham, Norfolk, newly elected vice-president, having returned to the meeting, was introduced to the Council by the President and addressed the Council as follows:

I apologize for being out of the room when I understand that I was called to be presented before you. While I had only been vice-president of the Society at that time a matter of about five minutes, I had already learned definitely (which I knew before) that I was a subordinate because Dr Bagg had requested that I leave the room and talk with him for a few minutes, which I did.

I appreciate the honor of being vice-president of the Society, not only personally, but because I know that I represent here as vice-president the Norfolk District Medical Society, which I have always been associated with and of which I am deeply fond. I trust that if there is anything I can do as vice-president to be helpful to Dr Bagg, he will request it. As I said a moment ago, I appreciate the honor, but also I assure you I realize its limitations. Thank you.

The President called on Dr John E Moran, Franklin, to report for a committee consisting of Drs Moran, Henry A Taddell, Hampshire, and Joseph Garland, Suffolk, appointed to draw up a resolution for presentation to the Council, stating the problem of sex criminality in Massachusetts and the need for its study.

Dr Moran presented the following resolution:

WHEREAS, This committee has been appointed by the president of the Society to draw up a resolution for presentation to the Council relative to "sexual psychopaths" and the problem of sexual psychopathy within the Commonwealth, and

WHEREAS, We as a committee recognize sexual psychopathy to be a condition wherein there is basically a constitutional personality defect frequently manifest by overt acts of a vicious nature against society, and

WHEREAS, We are of the opinion that the problem is not exclusively medical but is in large measure sociologic and penologic, therefore be it

RESOLVED, That the Massachusetts Medical Society take cognizance of the problem of sexual psychopathy and indicate its desire to co-operate, in any reasonable manner, in a study of the matter, and be it further

Resolved that a copy of this resolution be sent to the Recess Commission appointed to study the question of sexual psychopaths.

President O'Hara referred the resolution to the Committee on Mental Health, a subcommittee of the Committee on Public Health.

Dr Curtis C Tripp, Bristol South, presented the following letter from Dr David L Belding, Norfolk South, to the President:

The shortage of nurses has become one of the most pressing problems of present-day medicine. It is of vital importance to hospitals and private physicians. As such

it would seem to be the responsibility of the Massachusetts Medical Society to make a thorough study of this critical situation in order to formulate possible plans for its solution.

I am therefore asking you to present this matter to the Council, under "New Business" in order that, if the Council so decides, it may be referred for study to the appropriate committee.

Dr Tripp moved that this matter be referred to a committee by the President. The motion was seconded and carried, and the matter contained in Dr Belding's letter was referred to the Committee on Medical Education and Diplomas.

Dr Reginald Fitz, Suffolk, was recognized and moved that the President be authorized to appoint a committee to study the problems suggested by the resolution presented by Dr Sosman and report back to the Council. The motion was seconded.

Dr Sosman offered as a substitute motion that the President appoint a special committee, to include representatives of the Blue Cross, the Blue Shield, the Massachusetts Hospital Association, the Massachusetts Medical Society, the radiologists, the pathologists, the anesthesiologists and any other specialty groups concerned to define hospital services and medical services and to establish the proper relations between physicians and hospitals.

Dr Fitz having accepted this substitute motion, it was put to vote and was so ordered by vote of the Council.

#### COMMITTEE APPOINTMENTS

The President-Elect submitted a list of nominations to committees for the year 1947-1948. It was moved and seconded that the nominations be confirmed, and it was so ordered by vote of the Council.

There being no further business before the Council, the President declared the meeting adjourned at 10:30 p.m.

JOSEPH GARLAND, *Secretary*

#### APPENDIX NO 1

##### ATTENDANCE OF COUNCILORS

BARNSTABLE	Elizabeth Councilman
P P Henson	N F DeCesare
BERKSHIRE	H R Kurth
I S F Dodd	P J Look
P J Sullivan	R. C Norris
BRISTOL NORTH	G L Richardson
M E Johnson	F W Snow
W J Morse	ESSEX SOUTH
W M Stobbs	D S Clark
BRISTOL SOUTH	R E Foss
R B Butler	Loring Grimes
E D Gardner	C A Herrick
R H Goodwin	P P Johnson
William Mason	O S Pettingill
C C Tripp	E D Reynolds
Henry Wardle	J R Shaughnessey
ESSEX NORTH	H D Stebbins
E S Bagnall	P E Tivnan
R V Baketel	C F Twomey
R. E Blais	C A Worthen
G J Connor	FRANKLIN
	J E Moran

## HAMPSHIRE

F H. Allen  
E P. Bagg  
W A. R. Chapin  
A. J. Douglas  
E. C. Dubois  
F S. Hopkins  
A. G. Rice  
G. L. Schadt  
J. A. Seaman  
G. L. Steele

## HAMPSHIRE

L B. Pond

## MIDDLESEX EAST

Robert Dutton  
R. W. Layton  
K. L. MacLachlan  
R. R. Stratton

## MIDDLESEX NORTH

A. R. Gardner  
W F. Ryan  
W L. Twarog

## MIDDLESEX SOUTH

J M. Baty  
W O. Blanchard  
G F H. Bowers  
Madeline R. Brown  
R. W. Buck  
E. J. Butler  
J P. Casey  
C. W. Clark  
C. L. Denick  
J G. Downing  
C. W. Finnerty  
H. Q. Gallupe  
H. G. Giddings  
H. W. Godfrey  
J L. Golden  
A. D. Guthrie  
Eliot Hubbard, Jr  
F R. Joutet  
E. E. Kattwinkel  
A. A. Levi  
A. N. Makechnie  
R. A. McCarty  
J C. Merriam  
Dudley Merrill  
C. E. Mongan  
J P. Nelligan  
Dwight O'Hara  
Fabryan Packard  
L. S. Pilcher  
Max Ritvo  
E. R. Robbins  
M. J. Schlesinger  
H. P. Stevens  
C. B. Toppin  
C. P. Walcott  
A. L. Watkins  
Hovhannes Zovickian

## NORFOLK

B. E. Barton  
Carl Bearse  
G L. Doherty  
Albert Ehrenfried  
Susannah Friedman  
D L. Halberleben  
J B. Hall  
H. B. Harris  
R. J. Heffernan  
P J. Jakmaub  
L R. Jankelson  
C J. E. Kickham  
D L. Lionberger

D S. Luce  
C. M. Lydon  
H. L. McCarthy  
R. T. Monroe  
Hyman Morrison  
D J. Mullane  
W R. Ohler  
G W. Papen  
H C. Petterson  
H. A. Rice  
S A. Robbins  
D D. Scannell  
S L. Skvirsky  
J W. Spellman  
A R. Stagg  
N A. Welch  
P R. Withington  
E T. Wyman

## NORFOLK SOUTH

F A. Bartlett  
Harry Braverman  
D L. Belding  
W R. Helfrich  
E. K. Jenkins  
N R. Pillsbury  
D B. Reardon  
H A. Robinson  
R G. Vinal

## PLYMOUTH

C. C. Angley  
A L. Duncombe  
P H. Leavitt  
C D. McCann  
G A. Moore

## SUFFOLK

H. L. Albright  
A. W. Allen  
W H. Blanchard  
W J. Brinkley  
W E. Browne  
A M. Butler  
A. J. A. Campbell  
J F. Conlin  
Reginald Fitz  
Joseph Garland  
John Homans  
L. M. Hurxthal  
C. S. Keefe  
H. A. Kelly  
T H. Lanman  
C. C. Land  
Donald Munro  
R. N. Nye  
F R. Ober  
F W. O'Brien  
J P. O'Hare  
L E. Parkins  
L E. Phaneuf  
Helen S. Pittman  
W H. Robey  
H F. Root  
R. M. Smith  
M. C. Sosman  
Augustus Thorndike  
S N. Vose  
Conrad Wesselhoef

## WORCESTER

A. W. Atwood  
George Ballantyne  
F P. Bousquet  
E J. Crane  
G R. Dunlop  
W J. Elliott  
J M. Fallon  
L M. Felton  
Thomas Hunter

H. L. Kirkendall  
J A. Lundy  
D K. McClusky  
J M. Olson  
F A. O'Toole  
R. S. Perkins  
E. L. Richmond  
R F. Sullivan

J J. Tegelberg  
G C. Tully  
R J. Ward

## WORCESTER NORTH

J J. Curley  
J V. McHugh

## APPENDIX NO 2

## TREASURER'S REPORT

Return of members from the armed forces has been reflected in the increased income from dues during 1946 to \$51,752 from \$39,325 in 1945. Nonresident dues rose from \$1500 to \$1776. Income from the *New England Journal of Medicine* was \$9000 this year as compared with \$22,800 last year due to the mounting costs of publication. Income from censors fees rose from \$474 to \$1242, an indication that more new applicants are seeking membership in the Society. The Committee on Arrangements turned in an excess of income over expenses from the annual meeting of \$5268 and the New England Postgraduate Assembly a similar excess of \$823.

The Endowment Fund's income rose from \$498 to \$503 and the General Fund's from \$4527 to \$5162 but the Building Fund's dropped from \$2156 to \$1989. This can be attributed to the call of certain securities bearing a higher rate, or to their sale, in anticipation of call, to realize a better market price and to the sale of a few long term bonds to reinvest in convertible bonds of lower interest rate with an eye toward greater possibilities of profit in the future through their conversion features. However, in the Building Fund profit on sale of securities rose to \$591 in 1946 from \$173 in 1945, and profit from sales in the General Fund rose from \$591 to \$1898. The amount received from subscriptions to the *New England Journal of Medicine* from men in service fell from \$1312 to \$622, this total was paid over to the *Journal*.

Changes in the holdings of the General Fund resulted from the sale at profit of a number of separate bond issues of small denominations and reinvestment in larger unit holdings of two new bond offerings, both convertible into common stock—Dewey & Almy Co. 2 1/4's due 1976, and American Telephone and Telegraph Co. 2 1/4's due 1961. The following preferred stock shares were purchased during the year—50 shares U S Steel Co. 7 per cent cumulative, 100 shares Atlantic Refining Co. 4 per cent cumulative and 90 shares Monsanto Chemical Co. 3 1/4 per cent cumulative convertible.

The General Fund securities now represent a book value of \$179,094 as compared with \$142,689 in 1945.

The Building Fund securities stand at a book value of \$69,665, as compared with \$68,027 in 1945.

The Endowment Fund securities remain at the same book value as last year, \$23,166.

In summary, total revenue in 1946 was \$78,072 and total expenses \$52,046 leaving an excess of revenue over expenses of \$26,026.

Total Building Fund assets amount to \$73,117 an increase over last year of \$2580.

General Fund assets amount to \$238,152, an increase of \$26,953 over last year.

The Society ends 1946 with a grand total of assets in cash and securities of \$334,436 an increase of \$29,533 over 1945.

A breakdown of comparative expenses in 1945 and 1946 is appended. It is obvious that there has been a steady increase from \$33,133 in 1943 to \$52,046 in 1946 and a budget of \$64,195 for 1947. Plans are being considered which may well raise the annual expense figure for 1948 to over \$100,000. This makes an increase in the dues imperative.

It is hoped that with an increase in dues the Society will consider a larger refund to the district societies annually and also that, under guidance of the Committee on Finance the Society may consider pegging the total assets of the General Fund at a certain maximum figure and that, in any given year, after all expenses have been paid any income raising the General Fund above this figure be automatically diverted into the Building Fund. There is little to be gained by

indefinitely enlarging the General Fund, whereas the Building Fund stands not only for a potential much needed headquarters, but once the property has been acquired, stands back of it as an endowment, the income from which can be used to support the running of the establishment.

The year 1946 marks the ending of a long era of pleasant association between the Treasurer's Office and the staff of the *New England Journal of Medicine*. Now that the Society has developed its own clerical staff, the Treasurer would like to emphasize his appreciation for all past kindnesses and help given him by the *Journal* personnel.

#### COMPARATIVE EXPENSES, 1945 AND 1946

Salary	1945	1946
Secretary	\$3,000 00	\$3,500 00
Executive Secretary	4,000 00	4,400 00
Treasurer	2,000 00	2,250 00
<b>Expenses</b>		
President	608 77	154 39
Secretary	3,189 87	4,594 36
Treasurer	1,968 74	2,516 33
Delegates to A M A	818 86	3 380 01
Maintenance of Society Headquarters	3,746 33	4,078 63
Cotting luncheons	504 20	543 20
Refund to district societies	4,000 00	4,000 00
New England Council	100 00	100 00
Clerical	0	1,405 00
General administrative	2,509 80	4,701 22
N E J M for subscriptions to <i>Journal</i> from fellows in service	1,312 00	622 00
Shattuck Lecture	0	200 00
<b>Committees</b>		
Arrangements	272 15	0 (profit)
To Appoint a Director of Education and Information	0	14 55
Ethics and Discipline	143 20	147 41
Executive	287 74	246 80
Fee Schedule	0	689 48
Finance	20 23	3 00
Industrial Health	92 87	79 93
Legislation	3,580 02	3,841 73
Massachusetts Hospital Association	08	5 66
Maternal Welfare	3 16	0
Medical Defense	571 67	1,167 75
Membership	125 70	225 07
Military Postgraduate	607 63	52
Postwar Loan Fund	466 44	313 33
Postwar Planning		
General and sub-committees	2,440 84	4,084 04
Information Bureau	2,942 48	3,403 79
Postpayment Medical Care	8 66	0
Public Health	82 36	108 67
Public Relations	1,295 05	636 49
Publications (Directory)	1,709 00	3 12
Rehabilitation	44 10	0
Rules	4 51	0
To Study Malpractice Insurance	0	607 23
Tax-Supported Medical Care	47 21	22 53
War Participation	34 29	0
	\$42,537 96	\$52,046 24
<b>Expenses 1943</b>		\$33,133 02
<b>1944</b>		38,544 33
<b>Budget 1947</b>		64 195 00

#### APPENDIX NO 3

##### REPORT OF THE EXECUTIVE COMMITTEE

The Executive Committee of the Council met on April 23, 1947, in Sprague Hall, 8 Fenway, Boston, the meeting being called to order at 4 15 p m. Dr Dwight O'Hara, president of the Society, was in the chair.

Dr O'Hara spoke feelingly of the loss of Dr Tighe, secretary of the Society, on April 8, and asked those present to stand for a moment in silent tribute.

The record of the last meeting as submitted by the Secretary was then approved.

##### COMMITTEE REPORTS

###### Committee on Membership

This report, which had been circulated in mimeographed form, under date of March 19, was acted on by sections and accepted by unanimous vote.

###### Committee on Nominations

Dr O'Hara, referring again to the death of Dr Tighe, announced that he had appointed Dr Joseph Garland to fill Dr Tighe's unexpired term and had asked the Committee on Nominations to meet again on April 30 to propose names for secretary and vice-president, Dr Edmond F Cody having declined the latter nomination.

###### Treasurer's Report and Report of the Auditing Committee

Dr Eliot Hubbard, Jr, treasurer called attention to an error. The sentence reading "Total Building Fund assets amount to \$73,177, an increase over last year of \$2640," should read "— an increase over last year of \$2580." The Executive Committee recommends the adoption of this report as corrected, including the report of the Auditing Committee.

###### Committee on Ethics and Discipline

This report, for information only, is recommended for adoption by the Council. The Executive Committee commends the circular prepared under the auspices of the supervising censors for the instruction of candidates.

###### Committee on Public Relations

This report is divided into three items, the first two of which contain recommendations.

The first, a report of the Subcommittee on Insurance Relations, was accepted by the Committee on Public Relations, which recommended its acceptance by the Council, and the discharge of the subcommittee. The Executive Committee recommends the acceptance and approval of this report by the Council.

The second item concerns the establishment of a women's auxiliary to the Massachusetts Medical Society by the districts, at their pleasure, with the Committee on Public Relations aiding in the organization of these said units. The Executive Committee recommends that the Council accept this recommendation.

The third item concerns (a) the establishment of a Speaker's Bureau and (b) a discussion that took place at a meeting of the Essex North District Medical Society with reference to the payment of anesthetist's fees by the Blue Cross.

The Executive Committee recommends that the report as a whole be accepted by the Council.

###### Committee on Veterans' Affairs

In view of the continuing complications in the present relations between the Society and the Veterans Administration, the Executive Committee recommends the omission of the lines in this report calling for the discharge of the committee after the annual meeting.

###### Committee to Meet with General Hawley

It has become recently apparent that the method of co-operating with the Veterans Administration through a Blue Shield contract has been blocked, as the Massachusetts Medical Service does not deem it wise to handle this type of contract under existing conditions. As noted in the committee report, bills (H 950 and 137) filed by Massachusetts Medical Service and Blue Cross have been opposed by the American Legion and the Veterans of Foreign Wars, and reported three times unfavorably by the Insurance Committee.

The chairman of the Committee to Meet with General Hawley, Dr Humphrey L McCarthy, therefore recommends that the Massachusetts Medical Society deal directly with the Veterans Administration under a gentleman's agreement, similar to the Kansas Plan, rather than with a formal contract. To re-open this matter, three motions are necessary.

(1) To remove from the table, where it was placed by vote of the Council on October 2, 1946, the recommendation of the Executive Committee that the vote of the Council of April 10, 1946, in special meeting, be rescinded (This vote adopted the plan of a contractual arrangement between the Veterans Administration and the Blue Cross—Blue Shield, whereby the hospital expenses of veterans in civilian hospitals would be met by the Blue Cross as agent and whereby the costs of professional services of civilian physicians caring for veterans under the fee schedule would be met by the Blue Shield as agent.)

(2) To rescind the vote of April 10, 1946.

(3) To refer the whole matter back to the Committee to Meet with General Hawley for further negotiations along the lines of a gentleman's agreement, and report to the Council.

The Executive Committee recommends to the Council the adoption of these three motions.

#### Committee on Postgraduate Instruction

The Executive Committee calls special attention to the great service that this committee has rendered and recommends that its work be enthusiastically endorsed.

#### Joint Report of Committees on Rehabilitation and Industrial Health

The recommendation of these committees reads as follows: It was resolved that the joint Committee of Rehabilitation and Industrial Health agrees that there is a definite need for establishment of a community rehabilitation center and service in Boston in accordance with the Report of the Baruch Committee on Physical Medicine but that it should be established, maintained and controlled locally and not nationally, and that such a project is advisable.

The Executive Committee recognizes the desirability of such a rehabilitation center and recommends the acceptance of the committee report, with the suggestion that it be discussed before the Council by some authoritative individual.

#### OTHER BUSINESS

On motion of Dr. John E. Moran, Franklin President O'Hara appointed a committee consisting of Drs. Moran, Henry A. Taddell, Hampshire, and Joseph Garland, Suffolk, to draw up a resolution for presentation to the Council stating the problem of sex criminality in Massachusetts and the need for its study.

On motion by Dr. Kickham the Executive Committee tendered to Dr. O'Hara a vote of thanks for the wisdom and celerity with which he had conducted its meetings during the past year.

The Executive Committee adjourned at 5:45 p.m.

JOSEPH GARLAND  
Secretary pro tempore

#### APPENDIX NO. 4

##### REPORT OF THE COMMITTEE ON PUBLICATIONS

The Committee on Publications wishes at this time to report upon its supervision of the publication of the *New England Journal of Medicine* for the year 1946. We quote from the report of the managing editor, Dr. Robert N. Nye to the committee:

During the year 1946 the *New England Journal of Medicine* continued to expand, and the new regular and student subscriptions and the net gain in circulation were larger than ever before, the respective figures being 6783 and 3296, as compared with 5913 and 3203 in 1945. Since there were 4729 new regular subscribers and 823 transfers from "student" to "regular" but a net gain of only 2308 this means that the subscriptions of 3244 were canceled during the year. The loss of approximately 1000 of these subscribers is accounted for by canceled subscriptions from the Army and Navy, but that of the balance remains unexplained. Incidentally, the gain from the discharge of members of the Society from the armed forces about balanced the loss of Army and Navy subscriptions. As of December 26, 1946, *Journals* were being sent to 5380 members of the Society, 12,074 regular subscribers (including some members of the New Hampshire Medical Society), 3102 medical students, 345 members of the New Hampshire Medical Society (monthly) and 283 miscellaneous readers—a total of 21,384 copies, as compared with 18,088 at the end of 1945.

Publication costs were markedly increased during 1946 thus, whereas the total cost which includes printing,

binding, mailing and paper stock, was about \$76,500 in 1945 it increased to \$120,500 in 1946. Fortunately the revenue from advertising increased from \$73,900, to \$93,300 and that from subscriptions from \$66,300 to \$84,800 almost covered the greater publication cost, with the result that the *Journal* was able to pay to the Treasurer on December 31, 1946, the sum of \$9000, as compared with \$22,800 at the end of 1945. Since no money was advanced to the *Journal* by the Treasurer during 1946, this represents a clear profit. The actual profit was \$11,300, the balance being represented by an increase in surplus from \$15,800 to \$18,100.

During 1946, the editorial board considered 291 manuscripts, of which 201 or 69 per cent, were accepted. The corresponding figures in 1945 were 203 and 129.

Book paper is still scarce and of poor quality in fact, it is scarcer and of poorer quality than at any time during the war. In spite of the shortage, however, the number of text pages in 1946 was 1834 compared with 1508 in 1945. The reproduction of cuts has left much to be desired, but nothing can be done about it until a higher grade of paper is available. The majority of roentgenograms should be printed on coated stock, but this cannot be obtained. It is hoped that the paper situation will have improved by the end of the current year.

Although copies of the *Journal* are usually delivered to this office on the day following the date of publication, binding and mailing result in a delay of six or seven days before copies are received by members of the Society. This is unfortunate but practically unavoidable. In due course, it may be possible to cut the period to three or four days. The delay in the delivery of reprints is not so long as it was in 1945 but is still much longer than it should be possibly this can be corrected.

The decision of the Massachusetts Medical Society to employ its own stenographers has relieved the office staff of much work that interfered with an orderly routine. Furthermore, this has resulted in more office space for the work of the *Journal*. This increased space will suffice for a year or so, but even now hall again as much space is really needed. Telephone calls for the Society are still handled by the office staff, and since these comprise more than half the incoming calls, it seems only reasonable that, with an office force of its own the Society should have a separate switchboard.

Robert O. Leary has returned to his former position as one of the assistant editors after three and a half years in the Army. The relief of the managing editor is unbounded! Miss Davies and her staff have continued to handle the affairs of the *Journal* in a manner that is irreproachable.

The outlook for 1947 appears reasonably good. An abundance of manuscripts seems assured which permits the editorial board to exercise even higher standards of acceptance. An increase of circulation is anticipated particularly student subscriptions, inasmuch as a student representative of the *Journal* has been appointed in nearly all approved medical schools. A survey is now underway to determine, if possible, why a certain number of regular readers fail to renew their subscriptions. The cost of publication will be higher since the charges for printing, binding and mailing are to be increased 15 per cent on July 1, 1946 and on January 1, 1947 but since it is customary to permit all regular advertisers to continue for a year at former rates, the full effect of these increases will not be realized until after January 1, 1948.

An abstract of the auditors' reports is appended. The full report, signed by the auditors Hartshorn and Walter, is in the hands of the treasurer of the Society.

The Committee again records its deep appreciation of the services of Dr. Nye. His management of the *Journal* has given to the Society a publication of which it may justly be proud.

OLIVER COPE  
JOHN FALLON  
JAMES P. O'HARA  
CONRAD WESSELHOFF  
RICHARD M. SMITH, Chairman

ABSTRACT OF AUDITOR'S REPORTS

	1944	1945	1946
<b>Current assets</b>			
Cash	\$6,148.53	\$6,176.73	\$6,442.47
Accounts receivable	7,166.12	9,153.56	10,721.93
Capital assets	1,213.64	1,146.35	1,538.13
<b>Totals</b>	<b>\$14,528.29</b>	<b>\$16,476.64</b>	<b>\$18,702.53</b>
<b>Current liabilities</b>	<b>402.50</b>	<b>605.10</b>	<b>553.28</b>
<b>Surplus</b>	<b>\$14,125.79</b>	<b>\$15,871.54</b>	<b>\$18,149.25</b>
<b>Expenses</b>			
Publication of <i>Journal</i>	\$67,609.73	\$76,417.78	\$120,531.42
Publication of reprints	6,123.72	5,150.81	9,561.29
Office and other salaries	25,480.17	30,488.22	35,408.72
Commission fees, etc	5,478.47	7,893.93	8,756.49
Office and sundry expense	5,009.32	5,130.61	6,069.94
<b>Totals</b>	<b>\$102,701.41</b>	<b>\$125,081.35</b>	<b>\$180,327.86</b>
<b>Revenue</b>			
Advertising	\$38,271.40	\$73,852.44	\$93,345.21
Engraving	1,042.61	974.10	545.62
Reprints	4,389.43	6,194.49	9,712.16
Subscriptions (other than M M S)	55,978.15	66,278.18	84,792.33
Miscellaneous	2,083.06	2,327.89	3,210.25
<b>Totals</b>	<b>\$101,764.65</b>	<b>\$149,627.10</b>	<b>\$191,605.57</b>
<b>Net loss or profit to M M S</b>	<b>\$7,936.76 (loss)</b>	<b>\$24,545.75 (profit)</b>	<b>\$11,277.71 (profit)</b>
<b>Net publishing cost expenses minus (revenue minus subscriptions)</b>	<b>\$63,914.91</b>	<b>\$41,732.43</b>	<b>\$73,513.62</b>
<b>Average paid circulation</b>	<b>13,447</b>	<b>16,264</b>	<b>19,282</b>
<b>Net cost per subscriber</b>	<b>\$4.75</b>	<b>\$2.50</b>	<b>\$3.81</b>
<b>Net cost per member M M S (based on net loss)</b>	<b>1.81</b>		

Gynecology	8	0	8
Gynecology and obstetrics	62	10	72
Internal medicine	186	24	210
Internal medicine (allergy)	5	2	7
Internal medicine (arthritis)	4	1	5
Internal medicine (cardiology)	39	4	43
Internal medicine (diabetes)	4	0	4
Internal medicine (diseases of chest)	9	1	10
Internal medicine (endocrinology)	4	0	4
Internal medicine (gastroenterology)	12	1	13
Internal medicine (hematology)	5	0	5
Neurology	4	0	4
Neurology and psychiatry	40	12	52
Neurosurgery	8	4	12
Obstetrics	8	1	9
Ophthalmology	66	5	71
Ophthalmology and otolaryngology	69	8	77
Orthopedic surgery	50	9	59
Otolaryngology	64	7	71
Pathology	10	3	13
Pediatrics	40	4	44
Physical medicine	4	0	4
Physiotherapy (general practice)	2	0	2
Proctology	11	0	11
Psychiatry	12	1	13
Radiology	26	5	31
Roentgenology	29	4	33
Surgery, general	247	32	279
Surgery, general (gynecology)	10	1	11
Surgery, general (obstetrics)	9	0	9
Surgery, general (proctology)	8	1	9
Surgery, general (thoracic)	7	0	7
Urology	56	7	63
<b>Totals</b>	<b>2640</b>	<b>214</b>	<b>2854</b>
Hospital administrators			4
Public-health physicians			1
Nonresident physicians			40
Physicians refusing to participate			20
			3104
		Duplication	4
			3100

APPENDIX NO 5

REPORT OF THE COMMITTEE TO MEET WITH GENERAL HAWLEY

Last December, Part I of the fee schedule for medical services to the Veterans Administration was accepted and turned over to the Massachusetts Medical Service and signed as a contract. Since that time many things have happened

1 In the original plan, the procedure was to be as follows. The veteran requests treatment from the Veterans Administration in person or by letter, phone or telegram. If the Veterans Administration has no facilities available or if it would cause undue hardship for the veteran to report to a Veterans Administration facility, an authorization is sent to the Massachusetts Medical Service. The Massachusetts Medical Service issues a letter of eligibility to the veteran showing the number and type of treatments authorized. The veteran presents the letter of eligibility to any participating doctor. The doctor treats the veteran. At the end of month the doctor completes the treatment report and forwards a portion of the letter of eligibility to the Massachusetts Medical Service. The Massachusetts Medical Service pays the doctor if in order, and forwards the report of treatment to the Veterans Administration. At the end of month the Massachusetts Medical Service bills the Veterans Administration on a master voucher.

2. During the first part of December, 1946, approximately 6000 registration forms were sent to physicians in Massachusetts asking whether they desired to participate in the plan and whether or not their practice was chiefly concerned with a specialty. An analysis of the registration is as follows

CLASSIFICATION	CERTIFIED*	IN PROCESS	TOTAL
Allergy	8	3	11
Anesthesia	31	11	42
Cardiology	6	0	6
Dermatology and syphilology	33	5	38
Diabetes	4	0	4
Diseases of chest	12	2	14
Gastroenterology	5	3	8
General practice	1423	43	1466

\*Certified as a specialist only for the purpose of the Veterans Administration

3 On March 13, 1947, a letter from the Veterans Administration requested the Massachusetts Medical Society to assist the Veterans Administration in establishing for examination and treatment a list of specialists who meet the qualifications for specialists of the Veterans Administration. These qualifications were entirely new, and for those not possessing specialty-board certificates, the letter stated that the following data should be given

The number of years of experience in a given specialty (including recognized residencies),  
The percentage of practice devoted to a given specialty and whether the physician was recognized as a practicing specialist by the Society.

4 Within the past month, Massachusetts Medical Service has filed a bill (H 950), with a companion bill (H 137) under the name of Blue Cross, to give the combined agencies the privilege to sign contracts. Both these bills have been opposed by the American Legion and the Veterans of Foreign Wars, and reported three times unfavorably by the Committee of Insurance. Many conferences have been held with Blue Shield, the Veterans Administration and the veterans' organizations, as well as your committee, and the bill was rewritten (H 950) and has been agreed on by these various organizations and is now being considered in the House.

The outcome of this bill is not known, but the committee hopes that some pertinent information will be at hand in time for the Executive Committee. If Blue Shield is not granted this special power, they feel that they will not be able to handle this contract soundly.

Your committee is now working on a new type of program, which is a modification of the Kansas Plan, to have in readiness if the Massachusetts Medical Service deems it unwise to handle this type of contract.

The type of authorization that is being formulated cuts the paper work for the doctor to one page, but cannot be publicized until the contract is in effect.

5 On March 15, 1947, the committee received a new fee schedule from the Veterans Administration (No 10-2535a), which contains the maximum fees that the Veterans Administration will pay. No previous edition should be used.

JAMES KEENAN BRAGGER  
MICHAEL A. TIGHE  
HUMPHREY L. MCCARTHY, Chairman

## APPENDIX NO 6

## REPORT OF THE COMMITTEE ON POSTGRADUATE INSTRUCTION

Up until the present year, the activities of the Committee on Postgraduate Instruction have been part of the more widespread work of the Committee on Postwar Planning. For this reason, it has not been possible heretofore to present anything more than a mere outline of the work of this committee. Consequently, in order to bring all councilors up to date, the following brief historical review is presented.

In the spring of 1945, it was voted by the Committee on Postwar Planning (a) to provide postgraduate medical instruction for all Massachusetts physicians without charge and to arrange teaching schedules so as to make it unnecessary for any physician to travel more than a few miles, (b) to divide the state into teaching districts or circuits and to carry on identical programs in all teaching hospitals in any given district, and (c) to carry on in any given district under the guidance of a local committee.

On the basis of the above plan, the Commonwealth was subdivided into teaching circuits as follows: District No. 1—Pittsfield, Great Barrington, North Adams, District No. 2—Springfield, Holyoke, Northampton, Greenfield, District No. 3—Worcester and surrounding territory, District No. 4—Fitchburg, Gardner, Leominster, District No. 5—Lowell, Haverhill, Lawrence, Newburyport, District No. 6—New Bedford, Fall River and the Cape, District No. 7—North Shore and District No. 8—Greater Boston Area.

In attempting to satisfy the wants of the Greater Boston Area and with special reference to the needs of returning veterans, the Sanders Theater program was evolved. It is not necessary to review the history of the first Sanders Theater program given in the spring of 1946 all are agreed that it was a great success. Between 800 and 900 doctors registered for the series of lectures, and the average attendance for each exercise was about 400.

It is a pleasure at this point to direct attention to the fact that the concept of the Sanders Theater course came from Dr. Lewis Hurxthal. In addition, Dr. Hurxthal did most of the work in organizing the first program and in arranging for the many details involved in any such series of exercises.

In so far as the district programs for the 1945-1946 period are concerned, exercises were given in all districts with the exception of the Pittsfield and Fall River areas, Districts 1 and 6 respectively.

In retrospect, the year 1945-1946 was a period of trial and error but a year with enough success to justify going ahead. It took personal trips to all sections of the Commonwealth to set up local committees and to sound out the ideas of various groups. It also took many meetings of the committee to work out the details. But despite difficulties and certain errors in planning the concept of offering to various districts a series of exercises so planned as to make possible discussions by a team of instructors and to cover the Greater Boston Area with a series of lectures at Sanders Theater gained support and favor.

So much for past history. The work of the Committee on Postgraduate Instruction for 1946-1947 can be presented briefly as follows:

## District Programs

- District 1 (Pittsfield, Great Barrington, North Adams) — three exercises, eight instructors.
- District 2 (Springfield, Holyoke, Northampton, Greenfield) — three exercises, nine instructors.
- District 3 (Worcester and surrounding territory) — two exercises, six instructors.
- District 4 (Fitchburg, Gardner, Leominster) — three exercises, eight instructors.
- District 5 (Lowell, Haverhill, Lawrence, Newburyport) — three exercises, nine instructors.
- District 6 (New Bedford, Fall River and the Cape) — three exercises, nine instructors.
- District 7 (North Shore) — six exercises, twelve instructors.

Unfortunately we have no detailed account of the total number of physicians reached by these district programs. We can say that all exercises have been extremely well attended and, in addition, that many graduates of substandard schools have accepted this opportunity to take part in graduate study.

## Sanders Theater Exercises

As before, these meetings were under the able management of Dr. Hurxthal and his subcommittee. A series of ninety-two exercises were given by ninety-four instructors, covering a period of eight weeks. Total enrollment for the series was 1240 and the average attendance well over 500.

In other words, during the 1946-1947 season throughout Massachusetts not including Sanders Theater, a series of twenty-three exercises have been presented by sixty-one instructors. If we add to this the Sanders Theater exercises then the grand total for 1946-1947 is one hundred fifteen exercises conducted by one hundred fifty-five instructors. This is offered to the physicians of Massachusetts, including doctors in the armed services and residents and interns in various hospitals by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Health—all without charge.

## Budget and Expenses

All instructors are paid. Those who take part at Sanders Theater receive \$10 an exercise, and those who give instruction away from Boston receive \$25 for the first exercise and \$15 for subsequent exercises, the total amount for any one day not to exceed \$55 plus expenses. The budget allowed for 1946-1947 was \$3750 exclusive of the budget for the Bureau of Clinical Information. The Massachusetts Department of Public Health, after consultation with the committee regarding subject matter of certain programs, has been able to contribute \$1100 toward the work of postgraduate instruction. With this help we are sure to finish the year well within the total amount available.

## Bureau of Clinical Information

The Bureau of Clinical Information has continued to flourish under the able direction of Miss Mary D. Gaston. Although the service rendered to returning medical officers has naturally lessened, those who do seek aid present problems that are increasingly difficult to solve. The matters of location office space, home, equipment and hospital facilities are much less easy to answer than they were a year ago and if information of this sort could be made available to the Bureau by the district medical societies a more efficient job could be done in placing the right man in the right place. On the other hand a number of men have been placed as a result of inquiries received from an industrial firm, summer camps, a university state departments and town selectmen.

An increasing number of visiting physicians have made use of the Bureau. Indeed during 1946 physicians from twenty states and territories and from twelve foreign countries were interviewed.

The circulation of the *Bulletin* markedly increased nearly 9000 copies having been distributed as compared with about 5500 in the preceding year. Although these are most frequently used by individual physicians, many copies are forwarded to local and outlying hospitals and agencies. The *Bulletin* now lists monthly, quarterly and yearly meetings and all secretaries of medical clubs, associations and societies are earnestly requested to forward to the Bureau the dates and places of such meetings. Many conflicts of dates could be avoided if the *Bulletin* were consulted or the Bureau so informed.

## Recommendations for 1947-1948

So far as can be determined the present plan of postgraduate instruction has met with considerable favor. It is not contended that the plan is ideal. It is believed by the committee, however, that enough improvement can be made under the present organization to justify a continuation of the district programs for another year. Concerning the Sanders Theater exercises, no one has the answer. It was thought by many that this year's attendance would be less than that of last year. Such has not been the case. It is entirely possible that, with continued improvement, the Sanders Theater idea may become a fixture in the scheme of postgraduate instruction. At any rate in view of this year's experience, the committee feels entirely justified in recommending that these programs be continued another year.

W. RICHARD OHLER, Chairman



## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

#### CASE 33341

##### PRESENTATION OF CASE

An eighty-six-year-old woman entered the hospital because of vomiting.

For one year prior to admission the patient had had recurrent bouts of abdominal pain and vomiting, each lasting about a day. These became increasingly frequent until, after a particularly severe attack five weeks before admission, the patient entered another hospital, where a barium enema was said to have been negative. No gall-bladder or gastrointestinal x-ray films were taken. She had suffered from dyspnea, orthopnea and ankle edema for five months. She was discharged on digitalis and ferrous sulfate. The patient felt well until two days before admission to the Massachusetts General Hospital, when she experienced a recurrence of the vomiting, the next day she began to have severe cramping pain across the abdomen, with no radiation. There were no chills or fever, no rectal bleeding and no change in bowel habits. The appetite had been poor.

A bilateral salpingo-oophorectomy, appendectomy and removal of a uterine fibroid had been performed in 1901.

Physical examination revealed a debilitated, moderately dehydrated, ill appearing woman. The heart was enlarged, with a soft systolic murmur at the base. Occasional rales were heard at the lung bases. The abdomen was diffusely tender, particularly in the right upper quadrant. There was no spasm. The liver edge could be felt two fingerbreadths below the costal margin.

The blood pressure was 158 systolic, 60 diastolic.

Examination of the blood disclosed a white-cell count of 16,500, the urine contained an occasional white cell and many granular casts. A blood Hinton test was negative. The nonprotein nitrogen was 72 mg and the total protein 6.7 gm per 100 cc, and the chloride 106 milliequiv per liter. A chest plate showed dorsal scoliosis on the right and clear lung fields, the heart was at the upper limit of normal in size but was displaced to the left, and the aorta was calcified and tortuous. A film of the abdomen showed arthritis of the lumbar spine, a small amount of gas in the bowel without dilatation, no soft-tissue

masses or unusual areas of calcification and no free air under the diaphragm.

During the night the patient developed marked abdominal pain and tenderness and generalized spasm. Pelvic examination also showed diffuse tenderness. On the second day the patient became disoriented and had to be restrained. The temperature, which had previously been normal, rose to 102°F, the pulse to 100, and the respirations to 45. A stool specimen gave a ++ guaiac reaction. Some purulent exudate was recovered on abdominal tap, which on smear showed gram-positive cocci and bacilli. The patient was given penicillin, streptomycin, fluids and oxygen but continued to fail, dying on the third hospital day.

##### DIFFERENTIAL DIAGNOSIS

DR. PETER SARRIS: This eighty-six-year-old woman had had recurrent attacks of abdominal pain for a year. The attacks were often preceded by vomiting. In the differential diagnosis of an acute abdomen we realize that the history plays the most important role, and one tries to select the details that will give the clues to the final diagnosis. The age of the patient might influence us in the final diagnosis by making certain diseases less likely. Conversely, the age might confuse the case in that the history as given by an aged person is not always reliable. Also, one must bear in mind that a lesion is much likelier to be fatal at that age than in a younger person and in a shorter interval of time.

Important points are that the attacks were rather distinct, lasting about a day, and that the patient was apparently fairly well between attacks. It is stated, however, that she was debilitated. That may have been because of her age, the accumulated result of the insults produced by each one of these attacks or the progression of the underlying disease. No mention is made of the amount or character of the vomitus.

The severe attack five weeks prior to entry sheds some light in that the patient apparently recovered spontaneously and was well enough to be sent home. Presumably, then, the correct diagnosis was not made at that time, unless they thought that she could not stand surgery in spite of a correct diagnosis.

A barium enema was negative, and no Graham test or gastrointestinal series was done.

No mention is made about the red-cell count or hemoglobin or about anemia. The fact that the patient was discharged on digitalis and ferrous sulfate, however, indicates that the disease was associated with anemia.

The character and location of the pain are helpful, suggesting peristaltic pain across the abdomen, and either large-bowel or small-bowel spasm, or even biliary colic could have been responsible.

The absence of chills and fever or of rectal bleeding is helpful only in a negative way, and I do not

know whether the statement "no change in bowel habits" means during the attacks only.

We must accept the fact that a bilateral salpingo-oophorectomy and appendectomy had been performed, so that those organs can be eliminated as a direct cause of the disease. With the background of a previous operation, the story suggests small-bowel obstruction. A previous operation is, of course, not necessary for that diagnosis, since one third of all cases of small-bowel obstruction are not preceded by surgery.

The dyspnea, palpitation and ankle edema can be dismissed. They are significant but not so far as the diagnosis is concerned. They undoubtedly played a part in hastening death, but could not account for this picture. The blood pressure on admission indicates that the patient was not in shock — at least, the blood pressure was not remarkable. The white-cell count was 16,500, which is not helpful in the differential diagnosis. There were granular casts in the urine but no mention of albuminuria. I always thought that any number of granular casts should be accompanied by albuminuria, that also is not helpful in the differential diagnosis. The non-protein nitrogen of 72 mg per 100 cc could have been a result of a combination of nephrosclerosis and dehydration in a patient of that age but is not of specific help otherwise.

The chest film does not help. The plain film of the abdomen was negative so far as positive findings are concerned, I had hoped that we should get more evidence from it. There was a small amount of gas in the bowel. If it was in the large bowel, it means nothing, but in the small bowel, even though it is a small amount of gas, it may be significant, particularly if in repeat films the gas has increased. I should like to see the x-ray films. I see that a tube was put down, although the record does not mention that there was gastric drainage or what was obtained and how much.

Dr. STANLEY M. WYMAN: I believe that the gas lies in the small bowel, there are several loops of bowel in the left upper quadrant. They are at the upper limits of distention to be called definitely normal. It is more consistent with a picture of ileus. There is unusual calcification in the right upper quadrant.

I believe that that may well lie in the pleural cavity. That fact is not mentioned in the record, but it should have been. There is an unusually tortuous line of calcification in the right upper quadrant that is probably vascular, and slight calcification in the right upper quadrant seen below the large arc is about the expected location of the gall bladder. It suggests previous biliary disease, but it is not definite.

Dr. SARRIS: Is there any evidence of gas in the biliary tree?

Dr. WYMAN: I do not see any.

Dr. JOSEPH C. AUB: What is the dense area to the right of the tube?

Dr. WYMAN: I think that that is a fold of bowel.

Dr. SARRIS: There are no signs of gallstones throughout the gastrointestinal tract?

Dr. WYMAN: I do not see any.

Dr. SARRIS: Dr. Wyman's statement that there was gas in the small bowel bordering on the abnormal is helpful. It is important to know whether it was taken on admission or on a later day.

Dr. TRACY B. MALLORY: It was taken on the day of entry.

Dr. SARRIS: The final significant point is that an abdominal tap produced purulent material that on smear showed gram-positive cocci and bacilli, thus confirming the diagnosis of purulent peritonitis. Purulent peritonitis from an infarcted solid organ occurs late in the disease, and for that matter with a solid tumor, or a cyst twisting on its pedicle, the symptoms of infarction occur first and are followed by progression with secondary infection. I believe that the peritonitis came from a rupture of a hollow viscus — not from a perforated ulcer or perforated malignant tumor of the stomach, because I cannot visualize such distinct attacks caused by carcinoma of the stomach or attacks lasting only a day by an ulcer. The crampy nature of the pain is against that diagnosis, although pyloric stenosis occurs with crampy pain, preceded by vomiting.

Mesenteric thrombosis is fairly frequent at this age, ending with peritonitis, but it is not likely in this case because of the duration. It often causes premonitory symptoms, with minor attacks weeks before the final one, from thrombosis of minute vessels. I have not seen a case with distinct attacks for such a long period, and I believe that mesenteric thrombosis can be dismissed. Regional enteritis producing final perforation and peritonitis can also be discarded because the attacks were of such short duration. Acute mechanical small-bowel obstruction with strangulation is more difficult to dismiss. Recurrent attacks are not unusual, but I think that this patient had too many attacks for that. Usually, patients with acute small-bowel obstruction from adhesions — due either to a congenital band or to previous surgery or a Meckel's diverticulum — have only one or two preceding attacks and then get into trouble from gangrene. Carcinoma of the large bowel I shall dismiss, since there was no recorded change in bowel habits and the process was not progressive enough. Vomiting is not a prominent feature of carcinoma of the large bowel except late in the course of the disease. Carcinoma of the cecum can be associated with anemia but does not produce obstruction with obstructive pain, except terminally.

If this patient had had a Meckel's diverticulum, the chances are that it would have been discovered at the previous operation. Diverticulitis is a frequent cause of peritonitis in this age group, although

vomiting is seldom a prominent symptom of diverticulitis, which usually starts with fever. This patient was afebrile, and the attacks were of short duration.

Volvulus, particularly in the sigmoid, ends up with strangulation, infarction and peritonitis, but this patient had had too many attacks over a year for volvulus, the vomiting was too prominent, and the bowel symptoms were absent. The x-ray picture is not that of volvulus of the sigmoid. Recurrent intussusception from a small-bowel tumor such as a polyp is a definite possibility. Against it, however, is the fact that when a patient dies from one of these tumors with intussusception the evidence of small-bowel obstruction preceding it is much more definite than in this case. The intussuscepted bowel produces obstruction for a long enough time to cause dilated bowel before the infarction goes on sufficiently to perforate the bowel. I cannot exclude that diagnosis, however.

Biliary-tract disease must be seriously considered. The frequency of attacks of colic suggests a common-duct stone, especially in this age group. In younger patients recurring attacks of gallstone colic result from stones only in the gall bladder, but my experience has been that in older people when the disease is limited to the gall bladder it is frequently associated with perforation. If this patient had biliary-tract disease with such recurrent attacks, with a state of well being between attacks, common-duct stone would be the diagnosis. Although there were no chills, fever or jaundice, I cannot believe this woman had frequently recurrent gallstone colic from stones only in the gall bladder ending in an attack with perforation of that organ. One must assume common-duct stones along with it.

Gallstone ileus is a definite possibility because it accounts for the recurring attacks. These attacks could have been caused by either common-duct stones or the passage of many stones from a cholelithoduodenal or choledochojunal fistula, with crampy pain and vomiting. Finally, a large stone came down and bobbed around in the small bowel. There is evidence that it could finally have grown larger from the fecal concretions, and then produced the obstruction followed by perforation and peritonitis. The only thing against that is the fact that when gallstones perforate and cause general peritonitis, they are preceded for some time by intestinal obstruction.

Finally, carcinoma of the small bowel is rare, but whatever this patient died of is also probably infrequent. Of course, the fact that one expects an unusual case at these exercises does not justify the making of a rare diagnosis. The recurrent attacks are characteristic of cancer of the small bowel, which is a difficult diagnosis to make preoperatively. Vomiting preceding pain is a common story. Anemia, which I assume this patient had, is consistent with carcinoma. The lack of bowel symptoms

is more consistent with a small-bowel than with a large-bowel lesion. In the former the higher the lesion, the likelier it is to be carcinoma, and the lower down the likelier to be sarcoma.

I believe that this woman had general peritonitis from perforation of a hollow viscus. That is as far as I can go with any degree of certainty. To go beyond that and try to state the cause of the perforation one would have to resort to guesswork. Is there any description of blood cells in the aspirated fluid?

DR MALLORY: They are not mentioned.

DR SARRIS: In purulent peritonitis secondary to infarction there are numerous red cells along with the pus and bacteria.

I shall conclude by saying that my first diagnosis is carcinoma of the small bowel, with perforation and the second choice is biliary-tract disease, with gallstone ileus and perforation.

#### CLINICAL DIAGNOSES

Perforated viscus (? stomach or gall bladder)  
Generalized peritonitis

#### DR SARRIS'S DIAGNOSIS

Carcinoma of small bowel, with perforation?  
Biliary-tract disease, with gallstone ileus and perforation?

#### ANATOMICAL DIAGNOSES

*Carcinoma of gall bladder, with perforation*  
Cholelithiasis  
Choledocholithiasis  
General peritonitis  
Arteriosclerosis, generalized  
Calcareous aortic stenosis  
Hypertrophy of heart  
Nephrosclerosis

#### PATHOLOGICAL DISCUSSION

DR MALLORY: This was obviously a difficult case. The clinicians did not commit themselves any farther than a perforated viscus. Dr Sarris pointed a finger of suspicion to the biliary tree and also mentioned a carcinoma as a likely possibility, but he did not put the two together. That combination is what was found, however. The patient had a carcinoma of the gall bladder. Carcinoma of the gall bladder is found almost invariably in patients who have had gallstones for years. There were a great many stones within the bladder. A perforation had developed at the apex of the gall bladder, from which several stones had passed into the peritoneal cavity. There also was a chain of fourteen large, densely calcified stones in the common bile duct. I think that that beautiful arc-shaped line of calcification across the film represents the chain of stones.

As is usual in a patient eighty-six years of age, there were many incidental lesions. She had generalized arteriosclerosis, contracted kidneys, a hyper-

trophied heart, calcification of the aortic valve with a slight grade of aortic stenosis and, of course, generalized peritonitis

Dr. SARRIS Was there any evidence of a previous fistula?

Dr. MALLORY The gall bladder was adherent to the transverse colon, but there was no fistula

## CASE 33342

### PRESENTATION OF CASE

A seventy-seven-year-old retired sea captain was admitted to the hospital because of dyspnea and orthopnea

Fifteen years prior to admission the patient had had pleurisy and had spent nine months in a sanatorium. He was then free from chest symptoms until nine months before admission, when he developed a "lump" below the right nipple that broke down, discharged a cupful of pus and remained open until the time of admission. Areas of the sinus tract were biopsied and showed acute and chronic inflammation, with granulation tissue and foreign-body, giant-cell reaction. Smears were negative for acid-fast organisms, but guinea-pig inoculations were not carried out. An x-ray film of the chest at that time showed extensive calcification at both apices, particularly on the right. There was no definite cavitation. Calcifications were also noted in both hilar regions. The diaphragm was flattened on the right and adherent laterally to a markedly thickened pleura, which extended upward for a distance of about 10 cm. The margin of the pleura was irregularly calcified. Four months before admission the patient noticed the onset of dyspnea and orthopnea, both of which became increasingly severe until the time of admission, when merely the effort of sitting up in bed caused dyspnea. Three months before admission a persistent cough, productive of small amounts of yellow sputum, appeared. Two weeks before admission the discharge from the sinus increased, but the cough seemed to decrease slightly. At the same time frequency, nocturia and burning on urination, which had bothered the patient for about fifteen years, became much worse. During the two days prior to admission his general condition seemed much worse to his family, and a physician found the temperature to be 102°F.

Thirteen years before admission a transurethral prostatectomy had been performed because of the urinary symptoms mentioned above. These continued, however, and two years before admission, another transurethral resection was performed, with the diagnosis of fibrosis of the bladder neck. Four months before admission a biopsy of one of numerous small lesions on the face and forehead revealed a basal-cell carcinoma.

Physical examination showed a well developed but chronically ill man who was dyspneic on the

slightest exertion and somewhat disoriented. The skin showed a diffuse brownish discoloration. There were bilateral cataracts. The neck veins were distended. There were moist sticky rales throughout both lower-lung fields. There was edema and pigmentation of the ankles. The prostate gland was slightly enlarged, soft and tender.

The temperature was 101°F, the pulse 88, and the respirations 20. The blood pressure was 145 systolic, 85 diastolic.

Examination of the blood disclosed a red-cell count of 2,600,000, with a hemoglobin of 8 gm., and a white-cell count of 19,800, with 87 per cent neutrophils. The urine gave a ++ test for albumin, and the sediment contained innumerable white cells. Two sputum smears, three sputum concentrations, one gastric aspiration, one smear of material from the sinus tract and one concentration of the same material were negative for acid-fast bacilli. The total protein was 6.5 gm., the nonprotein nitrogen 44 mg per 100 cc., and the chloride 116 milliequiv per liter. Urine cultures grew out colonies of colon bacilli and pyocyanus bacilli, and those from the sinus tract, *Staphylococcus aureus* and a beta-hemolytic streptococcus. An x-ray film of the chest on the day of admission showed fluid in both pleural cavities and a granular increase in density throughout both lung fields, most prominent in the left midlung field.

During the hospital stay the temperature averaged 100°F, rising to 103 terminally, the pulse varied from 90 to 130, and the respirations from 20 to 40. Flatness and absent breath sounds developed at the right base, with bronchial breath sounds over the right middle lobe. On the eighth hospital day a chest film was described as not showing much change except a slight increase in the amount of fluid in the right side of the chest. The patient was given penicillin, sulfadiazine, fluids, Purodigin and oxygen and was put on constant bladder drainage. He did not do well, became gradually less responsive and died on the tenth hospital day.

### DIFFERENTIAL DIAGNOSIS

Dr. J. GORDON SCANNELL In this case an acute and chronic pleuropulmonary infection had extended through the chest wall and failed to heal. There was also evidence of a chronic urinary-tract infection, which I consider chiefly incidental, and a degree of cardiac insufficiency consistent with the patient's age and debilitating illness.

The three most frequent causes of empyema necessitatis, followed by persistent fistula, are tuberculosis, actinomycosis and a neglected empyema due to one of the usual pyogenic organisms. Although pyogenic organisms were cultured from the sinus tract, the natural history of the lesion leads me to suspect that they were secondary invaders rather than primary agents. Also to be considered are the generic causes of persistent fistulas — namely, can-

cer, foreign body (including the sequestrum of osteomyelitis), syphilis and other mycotic and granulomatous infections. We have little specific bacteriologic evidence to support any of these, although it is conceivable that as a sea captain, assuming his command to be of reasonable size, the patient was exposed to all kinds of exotic infections. I mention the matter chiefly to point out that in many regions, although not in this area, pulmonary calcifications are said to be accompanied more frequently by histoplasmin than by tuberculin sensitivity, certainly, such calcifications are becoming less and less synonymous with old acid-fast infection.

Of the usual causes of persistent fistula of the chest wall, certainly tuberculosis must be ruled out. It seems entirely reasonable that the patient had had a tuberculous infection in the past, even if the organism could not be demonstrated during the present illness. Although the evidence is of negative nature and hence may well be proved inadequate, I am inclined to accept it at its face value and assume, therefore, that this was not tuberculosis. I am influenced chiefly by the failure to find tubercles in biopsies of the sinus tract, in addition to the convincing evidence of negative sputum concentrations and negative gastric lavage, either or both of which should have been positive if this had been an overwhelming tuberculous infection.

In the absence of acid-fast infection, the likeliest diagnosis is actinomycosis. Here again we lack positive bacteriologic evidence, but it is my experience that such evidence is frequently obtained with difficulty, especially in the face of secondary infection, until adequate pathological specimens are obtained.

Before proceeding further, I should like to review the x-ray films. To my mind the remarkable thing about the films taken four months before entry is the relative lack of demonstrable disease except for the process in the right lower portion of the chest. There is certainly evidence of old pleurisy on this side, with narrowing of the interspaces and apparent pleural thickening with calcification, but it seems to me that there also is parenchymal involvement of the right middle, as well as of the right lower, lobe. The films after entry and just before death seem consistent with acute bronchopulmonary infection and edema. The increase of the right pleural pocket, however, and the granular density in the left mid-lung field, are noteworthy and consistent with the productive type of inflammatory lesion consequent on actinomycosis.

DR MILFORD D SCHULZ. In the film taken six months before entry the most striking point is evidence of old pleurisy at the right base, with calcification. The entire right side of the chest is smaller than the left, which can be accounted for on the same basis. Evidence of an old acid-fast infection is not impressive.

The film made at the time of entry shows a granular mottling in the central portions of the lung which can certainly have been due to pulmonary edema. There is some fluid in the right pleural sinus, which, on a subsequent examination, is seen to have become pocketed low in the posterolateral portion of the chest like an encapsulated empyema. There may be chronic pulmonary disease in the right lower portion of the chest, but most of the irregular areas of density seem to be part of the pleural calcification.

A spot film of the right lower portion of the chest shows deformity of one rib. Perhaps the calcification in the pleura was due to hemorrhage following trauma.

DR SCANNELL. The x-ray films do not help us particularly in arriving at a specific diagnosis. They suggest, however, an explanation for the rather marked symptoms of pulmonary insufficiency—namely, the cumulative effects of old chest trauma, with crippling of the bellows mechanism and fairly extensive senile emphysema.

To return to the specific chest-wall infection, however, although the x-ray films certainly do not of themselves suggest actinomycosis, they are compatible with that diagnosis. Chiefly in favor of it is the apparent disregard the process had for anatomic barriers and the complete lack of any anatomically circumscribed lesion. Failure to recover the organisms in the discharge is the only barrier to a positive clinical diagnosis. A more complete description of the nature of the sinus tract would have been helpful, since an actinomycotic fistula usually presents a rather characteristic type of purplish, indolent granulations, and often an ant-hill type of fistula. The hint about yellow sputum is an encouraging bit of evidence, and the note about the reciprocal relation between cough and sinus suggests a bronchopleural-cutaneous fistula that did not assume major proportions.

I am aware that I am discarding a number of physical findings in devoting the major portion of the discussion to the chest, but I believe that in this age group the catalogue of incidental pathological findings will parallel the diversity of the therapy. The immediate cause of death, in my opinion, was failing respiratory and cardiac reserve in a man with a crippled respiratory apparatus and a reduced oxygen-carrying capacity.

I believe that the primary disease was actinomycosis of the pleura, lungs and thoracic wall, with secondary infection. As subordinate diagnoses I include pulmonary edema and chronic pyelonephritis.

DR LEWIS K DAHL. Despite the x-ray reports, which were read as being more consistent with pneumonitis or pulmonary edema than with tuberculosis, the clinicians who saw this patient believed that he had an overwhelming tuberculous infection, probably tuberculous pneumonia. No organisms

were found by smear, however, on several examinations of the sputum, gastric aspirations and sinus drainage. Death occurred, of course, before bacteriologic confirmation of this diagnosis could have been expected.

I saw the patient terminally and agreed with the numerous predecessors, I was disturbed that a thorough search for actinomycosis had not been carried out.

#### CLINICAL DIAGNOSES

Pulmonary infection, probably active tuberculosis  
Sinus tract (? tuberculosis or from rib)  
Bronchopneumonia  
Benign prostatic hypertrophy  
Urinary-tract infection

#### DR SCANNELL'S DIAGNOSES

Actinomycosis of pleura, lungs and thoracic wall  
Pulmonary edema  
Chronic pyelonephritis

#### ANATOMICAL DIAGNOSES

Organizing pneumonia  
Chronic pneumonitis  
Acute glomerulonephritis  
Pulmonary edema and congestion

#### PATHOLOGICAL DISCUSSION

DR TRACY B. MALLORY. Dr Scannell has presented a persuasive case for actinomycosis. We naturally considered that diagnosis and did our best to substantiate it, but entirely without success. The right pleural cavity contained an old encapsulated empyema, and the left pleural cavity was entirely obliterated by fibrous adhesions. The lungs were

almost completely consolidated. The pleura over both lungs was thickened and fibrous, measuring up to 3 mm in places. At the left apex was an old puckered fibrous scar containing numerous small dilated bronchioles and much anthracotic pigment that was quite characteristic of a healed apical tuberculosis. There was no evidence of activity. The remainder of both upper lobes and about a third of each lower lobe were firm, noncrepitant and cut with difficulty, indicating diffuse fibrosis. The remaining lung tissue was markedly congested and edematous but still slightly crepitant. Microscopical examination showed all stages of organizing pneumonia from incipient lesions to dense fibrous scars. In many areas the persisting alveoli were partially epithelialized and contained many large phagocytes, filled with cholesterol vacuoles. Nothing suggestive of either tuberculosis or actinomycosis could be found.

The surprise of the autopsy was provided by the kidneys. Although not remarkable grossly, they showed on microscopical examination a severe grade of acute glomerulonephritis. It seemed probable, therefore, that renal insufficiency was an important factor in the immediate mechanism of death.

Little is known about the etiology of progressive organizing pneumonia. We have become increasingly aware of its importance in recent years. The clinical and x-ray pictures that it presents are readily confusable with pulmonary neoplasm, and consequently the surgeon is led to perform lobectomies or even pneumonectomies. In this case the presence of the acute glomerulonephritis suggests that the beta-hemolytic streptococci that were cultured during life were of more than coincidental importance. Whether they were the primary cause of the difficulty I cannot say from the evidence at hand.

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## Q FEVER IN THE UNITED STATES

ON PREVIOUS occasions mention has been made in these columns of the occurrence of Q fever and its relation to the nonbacterial pneumonias. The most recent reference<sup>1</sup> chiefly concerned a series of reports of circumscribed outbreaks of the disease that occurred in American and British military units in the Mediterranean area during the latter part of the war. Reference was made to outbreaks in this country that involved military units transferred from the Mediterranean Theater and laboratory workers engaged in the study of infectious material from the military units. In addition, a single case of Q fever acquired in Panama was mentioned.

It should be recalled that Q fever was first described as a severe influenza-like disease in Queensland, Australia, where it affected slaughterhouse workers, bushmen (foresters) and dairy workers

The causative agent there was found to be a filter-passing agent that was called *Rickettsia burneti*, and the reservoir of infection was shown to be the bandicoot, a rodent that is prevalent in the Australian bush. Certain ticks serve as vectors to transmit infection to man either directly from these rodents or through domestic animals that serve as intermediate hosts. The feces of ticks were found to be heavily infected with the rickettsias.

In the United States a similar if not identical agent was found in ticks collected from several northwestern and southwestern states, all the way from Washington to Texas. Isolated cases of infection have been reported in this area, and an outbreak occurred in the laboratories of the National Institute of Health, where the agent was being studied. Interestingly enough, the workers in the particular laboratory where the agent was being investigated were not involved, and it was thought that the infection was air borne by means of infected dust. That outbreak was the first in which pulmonary lesions similar to those of primary atypical pneumonia were described. A second outbreak has occurred at the same laboratory.<sup>2</sup>

The first sizable outbreak of Q fever acquired naturally in the United States has now been described in considerable detail. This occurred among stockyard and slaughterhouse workers in Amarillo, Texas. The circumstances under which it took place are of considerable interest, suggesting that similar outbreaks may be expected where cattle from endemic areas are slaughtered.

The epidemiologic aspects of this outbreak are quite revealing.<sup>3</sup> The cases all occurred among employees in a stockyard, its adjoining auction yards and a neighboring packing plant. There were 55 cases among 136 exposed persons. This is an attack rate of 40 per cent, which compares with the 50 per cent attack rates that were reported among the affected military units in the Mediterranean area. All the cases in this outbreak occurred between March 7 and 29, 1946, with 50 per cent of the cases in the stockyard workers beginning on or before March 10 and 50 per cent of those in the packing plant beginning on or before March 14.

A careful check of the sales' record revealed that only one lot of white-faced heifers, which were un-

loaded in the stockyard on February 23, could have fulfilled the requirement of having exposed all the categories of workers among whom the disease occurred. The known incubation period of the disease fitted perfectly: it was sixteen days from the day when this shipment was received to the day when 50 per cent of the cases began among the stockyard workers, and seventeen days had elapsed from the time when the slaughtering and processing of this lot of cattle began to the day when 50 per cent of the cases occurred in the packing plant employees. Among the latter, the attack rate among those engaged in killing the animals and in handling the freshly killed meat was 68 per cent, as compared with an 8 per cent attack rate among the remainder of the employees of the plant.

The actual mode of infection in this outbreak was not determined. No evidence was obtained to implicate an arthropod vector, and there was no evidence of person-to-person spread. Because of the explosive nature of the outbreak, and since evidence was obtained that afterward there were still a number of susceptible persons there, it was assumed that the infectious agent did not remain long in the packing plant. In the stockyard the epidemic lasted longer. The risk there involved all those handling live cattle, and although the first case among these employees occurred three days before the first case in the packing plant, the last occurred ten days after the outbreak in the packing company was over. It therefore appears that the infectious agent was present in the stockyards for a considerable period. It may have persisted in the dust, as suggested in the laboratory outbreak already mentioned, or it may have been deposited there from the excreta of cattle, since it is known to be present in the urine of experimentally infected animals and in the feces of the arthropod vectors. Another important feature of the outbreak is the fact that the disease was transmitted to stock handlers from apparently healthy cattle.

The clinical features of 18 cases that were studied were not unlike those described in the Mediterranean outbreak and among the infected laboratory workers.<sup>4</sup> There was great similarity in the general symptoms, with wide variations in their severity. The outstanding findings were a rather abrupt onset

associated with frontal headache, chilly sensations, general malaise, high fever of five to ten days' duration, essentially normal white-cell counts, roentgenographic evidence of soft, diffuse, patchy infiltrative lesions similar to those of primary atypical pneumonia, with minimal symptoms and signs referable to the respiratory tract, and a rapid and uneventful convalescence. There were practically no cutaneous lesions, the spleen was felt in only one case, and the lymph nodes were not enlarged.

Serologic tests were relied on to establish the diagnosis in almost every case.<sup>5</sup> Significant titers of complement-fixating antibodies were demonstrated with Q fever antigens during the second week after the onset of illness, in some cases, however, the highest titers were not reached before the fourth or fifth week. In most cases, high titers were maintained at least for a few weeks. Positive serologic confirmation was obtained in 49 of the 55 suspected cases. The complement-fixation tests were highly specific for Q fever, the same serums failing to show rises with endemic typhus or spotted-fever rickettsial antigens. Serums from unexposed persons, including household contacts of the cases, gave negative results. Some positive serologic results were obtained in a small group of presumably exposed persons, suggesting that there may have been unrecognized illness or inapparent infection.

Strains of rickettsia apparently identical with *Rickettsia burnetti* were isolated from the serums of 2 cases.<sup>6</sup> This was accomplished by workers in the virus and rickettsia division of the Lederle Laboratories. Although guinea pigs have generally been used for isolating the agent from human blood, the strains from this outbreak were obtained by passage through dilute brown agouti (dba) mice, which have already been found to be of value in studies of other viral and rickettsial diseases.

It is to be expected that Q fever will again be encountered in this country, and the experience in Australia suggests that the occurrence of this disease among persons who handle cattle that originate in endemic foci may be anticipated. Indeed, an outbreak of Q fever is alleged to have occurred recently in one of the Chicago packing plants, but details of this outbreak have not yet



been published. It may be difficult to detect the presence of infection in animals except by careful epidemiologic and serologic studies. It seems worth while, however, to make a survey among herds of cattle in an attempt to discover the various foci of this infection and to determine its mode of transmission in this country, with a view toward the development of methods for its control.

A report of a case of Q fever that was diagnosed in Boston but was acquired in Italy appears elsewhere in this issue of the *Journal*. This case emphasizes the importance of considering Q fever in the differential diagnosis of nonbacterial pneumonias in areas where the agent is known to occur and in persons who have been in such areas within the incubation period of the disease. Since the foci and reservoirs of infection of Q fever are not all known it is well to be on the alert for the occurrence of the disease in new localities. It should also be borne in mind that Q fever may manifest itself, as it usually does in Australia and perhaps in the Balkans, as a rather severe influenza-like infection with a more prolonged febrile course than that usually seen in influenza-virus infections but without evidence of pulmonary involvement.

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#### NEW ARMY MEDICAL CENTER

THE Office of the Surgeon General has released plans for the construction, by the Army Corps of Engineers, of the greatest medical research center in the world. This group of buildings, to be erected at Forest Glen, Maryland, at an initial cost of approximately \$40,000,000 will be equipped to anticipate and meet the medical problems of the future as well as to cope with those of the present—certainly a worthy and certainly an ambitious program.

The official designation of this imposing project is the Army Medical Research and Graduate Teaching Center. It will consist of a 1000-bed general hospital capable of expansion to 1500 beds, an administration building housing also the Army Medical Museum, a building for the Army Institute of Pathology, buildings constituting the Central Laboratory Group, a working library, staff quarters, an animal farm and other buildings.

The location at Forest Glen, just outside Washington, D. C., will provide a close relation to the Walter Reed General Hospital, the Navy Medical Center, the medical schools of Washington and the proposed Washington Medical Center. The Center will also have the advantage of co-operation with the National Bureau of Standards, the National Institute of Health and the National Research Council. Two hundred of its beds are to be specifically designated for research.

The Institute of Pathology will house the Department of Pathology, the American Registry of Pathology and the Army Medical Illustration Service. The Institute of Medicine and Surgery will house the departments of Research Medicine, Research Surgery, Research Dentistry, Veterinary Medicine, X-ray and Radiation, and Preventive Medicine. There will thus be brought together units from all over the country: the Medical Nutrition Laboratory from Chicago, the Medical Field Research Laboratory from Fort Knox, Kentucky, and the Surgical Research Unit from Fort Sam Houston, Texas.

Centralization is the keynote today, the medical centers that have sprung up and are springing up or would like to spring up are legion. Centralization, moreover, has tremendous advantages with its pooling of equipment and of administrative facilities and its opportunities for the exchange of ideas. It also has its disadvantages: a rigidity where flexibility is desirable and the stifling of individual enterprise, the Army never having been noted for its eager reception of new ideas. But such a splendidly conceived institution offers a great opportunity, and it is to be hoped that the Army will use this opportunity to its fullest advantage, without the traditional Army wastefulness of men and materials.

Stone walls do not a prison make, but neither do marble halls inspire original thinking unless freedom of thought and devotion to the truth are in the very mortar that binds their blocks together. Open minds as well as dollars must be put into the Army Medical Center. Originality seems to avoid conventional surroundings: radium came to us from a dilapidated shed in Paris, Sir Isaac Newton received the full impact of his epoch making apple while sitting under a tree, and Mr. Baruch is known to have given forth some of his most valuable ideas while sitting on a park bench in Washington.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**BAXTER**—G. Raymond Baxter, M.D. of Newton Center, died on July 24. He was in his fifty-third year.

Dr. Baxter received his degree from Tufts College Medical School in 1922. He was a fellow of the American Medical Association.

His widow survives.

**BLAIR**—Orren C. Blair, M.D. of Lynn, died on August 3. He was in his sixty-seventh year.

Dr. Blair received his degree from Harvard Medical School in 1903. He served on the surgical staff of the Lynn Hospital and was a fellow of the American College of Surgeons and the American Medical Association.

His widow, a son and a daughter survive.

**GILMAN**—Florence Gilman, M.D. of Northampton, died on August 1. She was in her seventieth year.

Dr. Gilman received her degree from Tufts College Medical School in 1903. She was formerly physician at Radcliffe and Smith colleges and assistant physician at Vassar College and was a fellow of the American Medical Association.

A niece survives.

**GOODALL**—Edwin B. Goodall, M.D. of Newton Center, died on August 6. He was in his sixty-sixth year.

Dr. Goodall received his degree from University of Maryland School of Medicine and College of Physicians and Surgeons in 1909. He was a member of the New England Ophthalmological Society and the American Academy of Ophthalmology and Oto-Laryngology.

His widow survives.

**NIGHTINGALE**—James Nightingale, M.D., of Worcester, died recently. He was in his seventy-second year.

Dr. Nightingale received his degree from Harvard Medical School in 1900. He was formerly medical director of the Jewish Home for Aged and Orphans and was a fellow of the American Medical Association.

An aunt and two nephews survive.

**ROY**—Joseph N. Roy, M.D., of Webster, died on March 19. He was in his seventy-fifth year.

Dr. Roy received his degree from Baltimore University School of Medicine in 1902. He was a fellow of the American Medical Association and an organizer of the Webster District Hospital.

His widow, a son and two daughters survive.

**WENTWORTH**—Arthur H. Wentworth, M.D., of Falmouth, died on July 30. He was in his eighty-fifth year.

Dr. Wentworth received his degree from Harvard Medical School in 1891. He was a former member of the Massachusetts Medical Society.

A daughter and seven grandchildren survive.

## MEDICOLEGAL ABSTRACT

**Hospitals** Applicability of the Massachusetts Labor Relations Act and the Federal Labor Management Relations Act. As a result of the decision of the Massachusetts court in *Saint Luke's Hospital v. Labor Relations Commission*, decided on November 30, 1946, and of the Labor Management Relations Act, enacted in 1947 by Congress over President Truman's veto, charitable hospitals in Massachusetts are in general exempt from the provisions of the state and federal labor-relations acts. The new Labor Management Relations Act by its definitions has excluded "any corporation or association operating a hospital if no part of the net earnings inures to the benefit of any private shareholder or individual." The Massachusetts Labor Relations Act contains no such provision, but the same result is accomplished by the decision of the Massachusetts court in the *Saint Luke's Hospital* case.

In that case the Laundry Workers, Dry Cleaners and Miscellaneous Workers of the Amalgamated Clothing Workers of America had sought certification by the Labor Relations Commission as the collective bargaining agency of certain nonprofessional employees of the hospital. The hospital sought the ruling of the courts whether or not the Massachusetts Labor Relations Act, on which the union was relying, applied to the hospital. The court held that the hospital was a public charity and not engaged in industry and trade and that therefore the act did not apply because it applied only to questions affecting industry or trade. The court declined to consider whether this same decision would be made if a hospital "were engaged in commercial undertakings, as the care and letting of realty or the conduct of a mercantile establishment, for the benefit of the hospital and employed persons in such undertakings."

Charitable hospitals should not infer from the decision or from their exemption under the new federal Labor Management Relations Act that it is illegal for their employees to join labor unions or even that the hospitals have an entirely free hand to take whatever steps they may see fit to attempt to prevent the unionization of their employees. For, although the rights and privileges that the state and national labor-relations acts give to employees generally do not now extend in Massachusetts to the employees of charitable hospitals, employers in Massachusetts were subject to some restraints in resisting the unionization of their employees even before those acts were passed.

## MISCELLANY

### RHEUMATIC FEVER RESEARCH

An announcement was made on July 7 of the formation of the Helen Hay Whitney Foundation for basic scientific research in rheumatic fever. The members of the distributing committee of the Foundation are Mrs. Charles S. Payson

(Joan Whitney), John Hay Whitney, Frederick K. Trask, Jr., and William Harding Jackson. Dr. T. Duckett Jones, of Boston, has been appointed medical director of the Foundation, with temporary offices in the New York Hospital, 525 East 68th Street, New York City. Dr. Jones, who has been granted a leave-of-absence from his positions at the Harvard Medical School and the House of the Good Samaritan, stated, "The purpose of the Foundation is to make possible research that may increase our knowledge of rheumatic fever—the leading fatal childhood disease."

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*The Unconquered Plague. A popular story of gonorrhea.* By Harry Wain, M.D., M.S.P.H. 12°, paper, 119 pp. New York: International Universities Press, 1947. \$1.50.

This small book, written for the laity, treats of the medical and social aspects of the disease. In order are considered the disease and its history, the gonococcus, its effects on men, women and children, its treatment and prophylaxis and gonorrhea as a social problem. The chapter on prostitution and sexual promiscuity could have been omitted without lessening the value of the book. A glossary and index complete the volume. The price is excessive.

*Pediatric Gynecology.* By Goodrich C. Schauffer, M.D., assistant professor of obstetrics and gynecology, University of Oregon Medical School, and visiting gynecologic surgeon and obstetrician, Multnomah Hospital, Portland, Oregon. Second edition. 8°, cloth, 380 pp., with 75 illustrations. Chicago: Year Book Publishers, Incorporated, 1947. \$6.00.

This second edition of a work first published in 1942 has been thoroughly revised to bring it up to date, and new material has been added in nearly every chapter. The section on gynecologic surgery in children has been expanded, and those on social service and medicolegal aspects have been considerably revised. Data on the use of penicillin have been incorporated throughout the text. The lists of commercial preparations of sex hormones and of state welfare agencies have been brought up to date. The sex problems of children, including masturbation, are discussed in the chapter on the external genitalia. The volume is well published in every way and should be in all medical libraries and in the libraries of gynecologists and pediatricians.

## NOTICES

### ANNOUNCEMENT

Dr. Benedict F. Massell announces the removal of his office to the House of the Good Samaritan, 25 Binney Street, Boston 15.

### SUFFOLK CENSORS' MEETING

The censors of the Suffolk District Medical Society will meet for the examination of candidates at the Boston Medical Library, 8 Fenway, on Thursday, December 4, at 4:00 p.m.

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, September 4, at 7:15 p.m., in the classroom of the Nurses' Residence. The subject "Sympathetic-Nervous-System Drugs, Old and New" will be discussed. Dr. Esther E. Bartlett will be chairman.

## GRANTS AND FELLOWSHIPS IN CANCER RESEARCH

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is entertaining applications for grants and fellowships. Applications for extension of existing grants in cancer research will be received until October 1, and applications for new grants until November 1. Applications for fellowships and senior fellowships in cancer research may be submitted until December 1.

Final decision on applications submitted during this period will be made in most cases soon after February 1. The grants ordinarily will become effective on July 1, 1948. Fellowships may begin at any time determined by the committee, although ordinarily these also will take effect on July 1.

During the last two years the American Cancer Society, acting on the recommendation of the Committee on Growth, has awarded one hundred and seventy-six grants and forty-seven fellowships, representing a total expenditure of some \$2,700,000. The committee will continue to recommend support of biologic and clinical research dealing broadly with phenomena relating to growth, typical or neoplastic. In the formulation of this program the committee will be guided, as in the past, by the advice of some one hundred and twenty scientists grouped in twenty panels, comprising its sections on Biology, Chemistry, Physics, Chemotherapy, Clinical Investigation and Fellowships.

Communications regarding grants or fellowships should be addressed to the Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N.W., Washington 25, D.C.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 28

WEDNESDAY, September 3

\*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

\*Open to the medical profession

SEPTEMBER 2-6 American Congress of Physical Medicine Page 610, issue of April 17

SEPTEMBER 2-7 International Cancer Research Congress Page 340, issue of February 27

SEPTEMBER 4 New England Hospital for Women and Children Notice above

SEPTEMBER 8-12 Third American Congress on Obstetrics and Gynecology Page 340, issue of February 27

SEPTEMBER 8-12 American College of Surgeons Page xv, issue of August 14

SEPTEMBER 11 Recent Advances in the Treatment of Infectious Diseases Dr. Conrad Wesselschoeff Pentucket Association of Physicians 8:30 p.m. Haverhill

OCTOBER 6-10 American Public Health Association Page 456, issue of March 20

OCTOBER 13-18 Medicolegal Conference and Seminar for Pathologists, Medical Examiners and Coroners Page 242, issue of August 14

OCTOBER 29-31 New England Postgraduate Assembly Copley Plaza Hotel Boston

FEBRUARY 6 American Board of Obstetrics and Gynecology Page 242, issue of August 14

APRIL 19-23 American College of Physicians Page xiii, issue of July 31

MAY 6-8 American Association for the Study of Goiter Page xiii, issue of July 31

MAY 11-15 American Association on Mental Deficiency Page 146, issue of July 24

### DISTRICT MEDICAL SOCIETIES

#### NORFOLK

SEPTEMBER 23 Boston University Night

OCTOBER 28 Lahey Clinic Night

NOVEMBER 25 Tufts Night

JANUARY 27 Round-Table Discussion Bleeding from the Alimentary Tract

FEBRUARY 24 Obstetric and Gynecologic Night

MARCH 23 Harvard Night

#### SUFFOLK

DECEMBER 4 Censors' Meeting

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## TRAUMATIC ARTERIAL VASOSPASM

PHILIP S FOISIE, M.D.\*

BOSTON

THE opportunity of treating a large number of war wounds of the extremities has demonstrated that vasospasm, of varying intensity and obstinacy, often complicates these injuries. This paper is not primarily concerned with cases of sub-total ischemia in which the immediate viability of the part is threatened but with the less dramatic and much larger group in which the persistence of a relatively low-grade arterial spasm is likely to cause nutritional changes adversely affecting the functional result.

Everyone is alarmed when a wound involves or suggests injury to a major artery, modern surgeons are equally apprehensive about the cold, pulseless limb produced by a widespread and intense arterial spasm, of which there have been many reports in recent years. Too little concern, however, is generally shown about the more moderate picture of arterial spasm, which holds little or no threat to the viability of the limb but a serious one to the ultimate function. In my opinion some of these unsatisfactory functional results are not entirely unavoidable. They have been explained by diagnoses of traumatic arthritis, Sudek's atrophy, neurotrophic edema and other titles to fit the prominence of certain signs found in the so-called "causal states," and thus the surgeon has considered himself absolved of responsibility for the functional result. An impaired arterial blood supply due to a sub-acute arterial spasm is regarded as the fundamental cause of much disability not inherent in the original injury. Recognition of the ischemia and rational specific therapy are essential to proper treatment.

### INCIDENCE AND PREDISPOSING FACTORS

Although actual percentage figures of the occurrence of vasospasm in war injuries are not available, the clinical experience of one particularly interested in this phenomenon is not without value. In a hospital averaging 1500 war casualties, of which about 85 per cent were surgical, and excluding cases of trench foot (all of which presented some degree of

vasospasm at one stage of the disease), an average of 12 to 15 cases were constantly being watched and treated for vasospasm that was considered sufficiently pronounced to endanger the functional result.

From this experience, can any conclusion be reached regarding what sort of injury is likely to be complicated by arterial spasm? Are the increased wartime incidence and interest in this and allied disorders due to anything peculiar to battle casualties, and what application is there to civil practice? These questions are considered under the following headings: the extent and location of the initial injury, the tissues involved, individual susceptibility, and blast effect.

### Extent and Location of Original Injury

Contrary to what might be expected, the incidence of arterial spasm does not parallel the severity of the original wound. Patients with extensive wounds involving shattering compound fractures, with much soft-tissue destruction of the upper portion of an extremity, may have quite adequate circulation in the distal portion of the same limb, whereas minor injuries to toes or fingers may set up a vasospasm so severe as to threaten function. Wounds were often seen with such extensive loss of substance as to make one wonder how sufficient circulation could get through to the distal portion, and yet the circulation there was found to be adequate. In 1 case, in spite of extensive loss of substance in a wound of the elbow, no clinical evidence of vasospasm appeared, and the circulation to the distal portion of the extremity remained adequate (Fig 1).

In another case a shell fragment tore through the upper extremity, taking with it the greater portion of the humerus (Fig 2). In spite of the soft-tissue destruction obviously involved, the circulation to the forearm and hand remained adequate. It should be noted that in these extensive injuries the wound is wide open — thoroughly decompressed. This factor is discussed below.

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Conversely, some of the most stubborn cases of vasospasm complicated mild injuries. A patient whose only injury was a bullet wound through the proximal phalanx of the left little finger that healed promptly, but with some deformity and a tender scar, developed such persistent vasospasm that dorsal ganglionectomy was required after all other

teries have a natural tendency to contract to prevent excessive blood loss and that vasospasm is produced by the sympathetic system. It is logical, therefore, to look for direct trauma to large arteries or nerves in attempting to analyze the cause of vasospasm. Many reported cases with direct trauma, particularly to large arteries, have been complicated by extensive spasm. This is not, however, an essential part of the mechanism, and in the cases presented below, there was often no evidence of direct injury to main arteries or nerves. Illustrative of this are the 2 cases in which the injuries were confined to digits, with no possibility of direct trauma to important arteries or nerves but which presented stubborn vasospasm. In other cases, although the site of the wounds did

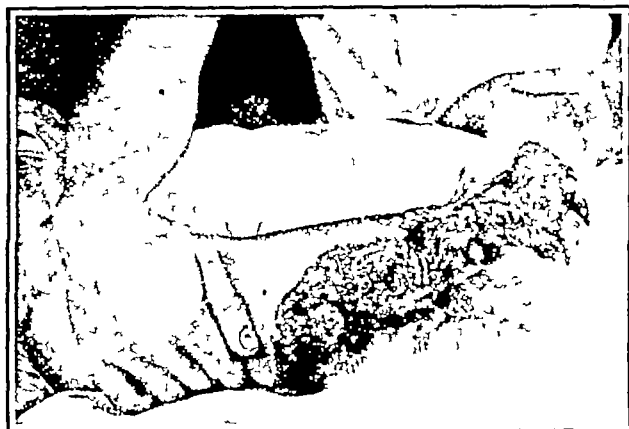


FIGURE 1 *Photograph of a Shell-Fragment Wound of the Right Arm*

*Despite extensive soft-tissue injury, circulation remained adequate*

efforts to restore circulation had failed. After this operation good circulation was restored, and the patient regained full function of the hand and fingers. This case is reported in detail below. Another patient was injured by a small shell fragment, which passed between the first and second toes of the left foot, causing mild wounds to the adjacent sides of the two digits. A week later the wounds were healed, but the foot was cold and cyanotic. So obstinate was the vasospasm that after all measures for vasodilatation, including repeated sympathetic blocks, had given only temporary relief, lumbar ganglionectomy was done two and a half months after injury, and the arterial supply subsequently remained adequate.

My experience is that the incidence of vasospasm does not rise with the severity of the wound but is found oftener in the smaller, quickly closed wounds than in the larger, wide-open ones. This suggests that tension is a factor and may explain the fact that a certain measure of success attended the decompression of early Volkmann's contracture by multiple, long incisions in the period when that complication was attributed to venous congestion. Although I am convinced that the proximate mechanism of Volkmann's contracture is an intense arterial spasm,<sup>1</sup> increased tissue tension may be a factor in the spasm.

#### *Tissues Involved*

Most people associate arterial spasm with injury to arteries or nerves. It is known that injured ar-



FIGURE 2 *Roentgenogram of a Shell-Fragment Wound of the Shoulder and Arm*

*Despite extensive loss of tissue, including the greater part of the humerus, circulation to the forearm remained adequate*

not offer such absolute preclusion of artery or nerve injury, evidence in favor of such injury was not usually found. Wounds from flying shell fragments followed no pattern and were seen in all locations, courses and degrees of severity—the impression that such factors influenced the incidence of vasospasm was not gained.

#### *Individual Susceptibility*

In an analysis of this sort, a predisposition of the patient must be considered at least briefly. There is

something to be said for such a possibility. Some people, even in the best of health, often suffer from cold extremities due to vasomotor lability. If to this is added the rigors of battlefront conditions before injury—physical and nervous exhaustion, deficiencies of diet and body hygiene and all grades of exposure to the elements—some element of predisposition cannot be denied.

### *Blast Effect*

So far, rather negative conclusions have been reached, but one factor that may for the moment be called the "blast effect" is, in my opinion, positive. An appreciable number of self-inflicted wounds were treated. In these cases the first and second toes of the left foot were most frequently injured. Occasionally, a more determined or a less careful patient had blasted through the metatarsal region. Since these patients were usually in no particular hurry to be rehabilitated, their slow progress was at first attributed to lack of co-operation in active exercises. It was soon realized that in this type of wound the incidence of vasospasm was high—in fact, to some degree at least, almost universal.

In such close-range wounds the blast effect or concussion was obviously severe, with diffuse intracellular damage. Vasospasm has been noted in the so-called "crush syndrome" (Bywaters<sup>2</sup>). In fact, in a case in which the leg had been crushed in an air raid, vasospasm of the opposite, uninjured leg resulted in the loss of two toes.<sup>3</sup> This mechanism may be operative to some extent in so-called "winger injury."

On the basis of the high incidence of vasospasm in cases in which the blast factor is heavy, it can perhaps be understood why war injuries, which are largely caused by ragged, irregular shell fragments propelled by high-explosive forces, are more frequently complicated by vasospasm than civil accidents. In 1935 Montgomery and Ireland<sup>4</sup> published a review of the literature in which they reported 44 cases of "traumatic segmentary arterial spasm" resulting from all kinds of trauma, of which 26 were the result of gunshot or high-explosive injuries. The comparatively smaller penetrating or perforating wounds probably cause more blast effect, at least on the remaining tissue, than the larger evulsing wounds, which are also decompressing.

In my experience the incidence of vasospasm is not dependent on the extent or location of the injury, or particularly on the structures involved, it is higher in the less open wounds, some predisposition may be operative, and diffuse tissue damage due to the concussive effect of explosive missiles is a factor.

### CLINICAL PICTURE

In traumatized extremities vasospasm has been found in all degrees of intensity and distribution. This paper is concerned particularly with the less

severe grades that might escape the unobservant. An example of arterial spasm in its simplest form occurred in a soldier who had suffered a rather minor soft-tissue wound over the proximal portion of the dorsum of the right foot that had nearly healed. Inspection of the foot revealed a striking and most unusual color change. The medial half of the dorsum of the foot, including the first and second toes, was blanched to a dead white, in contrast with the normal pink of the lateral half and the fourth and fifth toes—the third toe showed partial

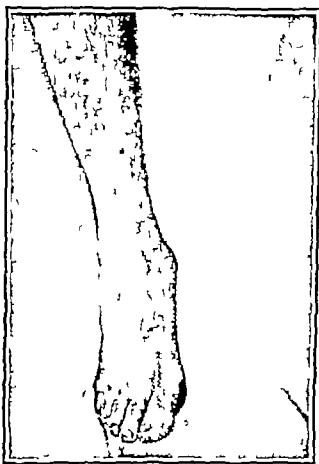


FIGURE 3 Photograph Illustrating Vasospastic Ischemia Secondary to a Penetrating Wound of the Calf. The three white areas are finger pressure spots. Note the irregular blanching particularly in the distal portion of the foot.

changes. On palpation the blanched area was cold, and the pink area was warm, tactile sensation was less acute in the affected portion. The extremity constituted almost an arteriogram of occlusion of the dorsalis pedis artery—substantiated by an absent pulse in that vessel. The ward officer and the patient had noticed the condition for at least two or three days but had not been aware of any difficulty before that time. Treatment of any sort was postponed so that pictures could be made to record such a precisely demarcated example of arterial block, but they were never made. The next morning the foot was quite normal, and no recurrence took place—it was not possible to stimulate one even for the record. There was no intrinsic damage to the dorsalis pedis artery, which had been caught in a segmentary reflex spasm stimulated by some impulse from the nearby injury. Although most complete and sharply defined while in effect, it was

transient, and its spontaneous disappearance was equally complete. This case is not regarded as involving any threat to the ultimate function of this particular foot but rather as a classic example of arterial spasm in its simplest form. It is the element of which the more extensive and more obstinate syndromes are composed. The prominent features of such a picture are of interest.

Color change is the outstanding sign. It varies under different conditions but always differs from that in the opposite member. At room temperature and at rest the color is a combination of pallor and cyanosis (Fig 3). The pallor is usually spotty,

An interesting group of symptoms is that based on the common denominator of local discomfort. Unlike the complaints in the true causalgias, severe pain is rare, although moderate degrees of pain may occur. The patient often complains of numbness, coldness, tingling or other such descriptive paresthesias but is reasonably comfortable so long as the extremity is supported and at rest. There is local tenderness, out of proportion, it may seem, to the force of palpation — indeed, even the threat of palpation is poorly received. The patient's guard is always up — a picket line that ward attendants and fellow patients soon learn not to cross. The ex-



FIGURE 4 Roentgenograms of Both Feet of a Patient with a Compound Fracture of Both Bones of the Right Lower Leg

*This patient had signs of vasospastic ischemia when seen five months after injury. Note the osteoporosis in the bones of the right foot (right).*

whereas the cyanosis is diffuse, increasing distally in depth. As compared to the opposite side the lack of red tones is distinctive. With dependency or exposure to cold, particularly on wet days out of doors, the cyanosis increases, and with elevation it fades and pallor increases. The extremity actually looks cold.

The surface temperature is obviously decreased, being lowest distally. Sometimes the patient volunteers this as a subjective complaint. The lower surface temperature is easily noticed by a comparison of palpation with that on the other side or the proximal part of the same extremity. All grades from a barely perceptible difference to a definite chill have been observed. Almost a part of the cool sensation is that of dampness — a combination sufficiently unpleasant to arrest attention and interest.

Swelling is generally seen in all injuries, particularly on use and dependency after plaster immobilization. Cases presenting ischemia are no exception. Anoxemia increases permeability of the capillary walls and increases interstitial fluid. The amount of fluid thus caused, however, is not large, and unless other factors contribute, edema is moderate.

the extremity is held immobile, with the joints flexed. There is a disinclination to exercise and a disapproval of any manipulation. This symptom complex in itself retards rehabilitation and may make one suspect the patient of poor co-operation.

Finally, the most specific, reliable and convincing sign of arterial spasm is the finding of diminished or absent peripheral pulses, complemented by adequate pulses on the alternate side and variably responsive to measures of vasodilatation. The parallel between the observable evidence of ischemia and the lowered pulse volume is reasonably consistent.

#### VASOSPASM AS A SPECIFIC ENTITY

Of course, vasospasm is not accountable for all circulatory deficiencies following injury. Swelling and cyanosis are usual after fractures, particularly during the initial mobilization period. Impaired venous return and the softening of disuse and lowered local metabolism must be overcome in all injuries of any moment. Beyond this, however, the careful observer will find that in some cases a definite deficiency exists on the arterial side, the swelling is less prominent, the cyanosis contains more pallor and less redness, the surface temperature is lower,

there is more discomfort, and the distal pulse is diminished or absent. Although arterial spasm probably occurs oftener in war wounds it seems to complicate certain civil injuries more frequently than may have been suspected. All grades of severity and of extension are possible, and the development can be insidious. Arteriospasm has probably been overlooked at times, or its results attributed to other causes.

Blackwood<sup>3</sup> presents the following description:

The arteries are the supply lines. An ischemic limb resembles the inhabitants of a beleaguered town. With

blood supply is of primary importance for repair of injury and for maintaining good tone of the extremity pending return of function. Arterial spasm complicating injury throttles a blood supply that needs to be at its best.

#### THERAPY

So far as possible, cases presenting vasospastic ischemia were grouped together. It was believed that both the patients and the ward personnel could more easily be indoctrinated in the general program and the results better evaluated. Basically, blood

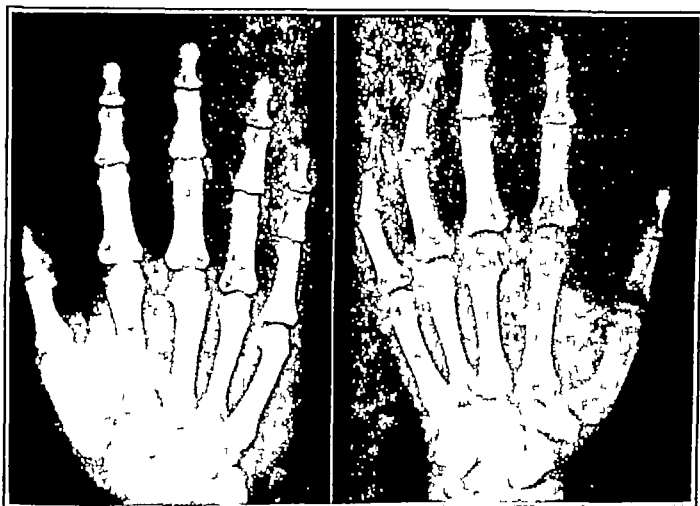


FIGURE 5 Roentgenograms of Both Hands Taken Three Months after the Patient Sustained a Shell Fragment Wound of the Upper Right Arm, with No Fracture or Nerve Injury.

The hand was still cold and blue. Note the decalcification, the haziness of joints, the atrophy of the soft parts and the flexion of fingers of the right hand (right) as compared with those of the normal hand (left).

supplies diminished or cut off they can keep up normal appearances for a time, but soon they begin to starve. They feel cold, their faces are pale or blue, they become less active and as conditions grow worse they become apathetic, or complain loudly to those in authority. In the human limb there is absence of arterial pulsations, lowering of surface temperature, pallor or cyanosis, anesthesias and pain.

As stated above, this report is not primarily concerned with the limbs whose lines have been completely cut off but rather with those that are on short rations. Malnutrition, which is the basic difficulty, results in degenerative changes of the musculoskeletal system primarily. Muscle atrophy, osteoporosis, limited and painful motion, flexion deformities and joint stiffness are the price of a prolonged arterial inadequacy (Fig. 4 and 5). A rich

loss and dehydration were corrected, and adequate diet, added vitamins and sufficient rest assured. Some patients received 4 gm. of aspirin a day and 30 cc. of whisky three times a day, but no improvement was noted from this medication. Buerger's exercises were used routinely, without relief of the arterial spasm. The extremities were kept warm but not overheated (these patients were not allowed beds near the stoves), and exposure to cold and inclement weather was avoided. Heaters to other parts of the body were used, and warm (not hot) soaks were given to the affected parts several times a day.

Paravertebral novocain blocks, which were employed as soon as the condition was observed, al-



most universally caused improvement for at least a short time—even if only for a couple of hours. More frequently, such improvement lasted for two or three days. Blocks were repeated several times if necessary and so long as improvement increased

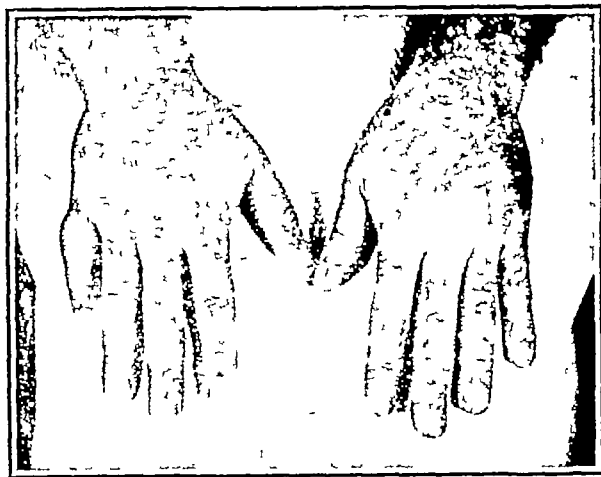


FIGURE 6 Photograph of Both Hands of a Patient Presenting Vasospastic Ischemia (Case 1)

Note the moderate swelling and cyanosis of the right hand, which was also cool

with successive blocks. If the interval of improvement decreased progressively, ganglionectomy was considered. This operation was done in 4 cases in which vasospasm persisted beyond all the treatment

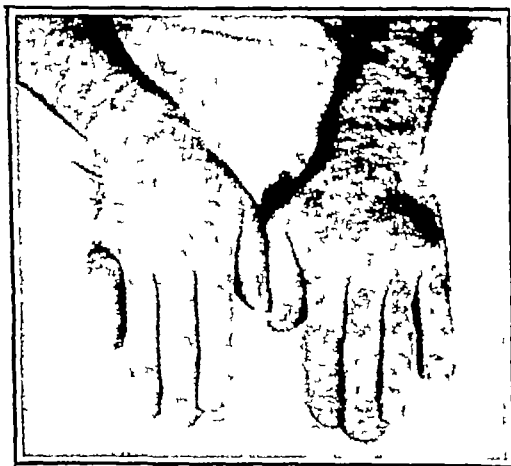


FIGURE 7 Photograph of the Same Hands after Right Upper Dorsal Ganglionectomy

The cyanosis and swelling have disappeared. After initial marked vasodilatation, the hand took on a normal color

mentioned above, and in each case permanent relief of symptoms resulted

#### CASE REPORTS

The following cases of persistent low-grade vasospasm illustrate the difficulties sometimes encountered

**CASE 1** J C, a private first class, while in close fighting in France on June 14, 1944, sustained a bullet wound of the right fifth finger and was struck on the forehead by the stock of an enemy rifle. He was not unconscious. On the same day he was admitted to a field hospital, where the finger wound was débrided. He was evacuated by air to England, arriving at a general hospital on June 17. At that time a lacerated wound in the center of the forehead was found, x-ray examination of the skull was negative. A perforating rifle wound, whose entrance was on the dorsum of the proximal phalanx of the right fifth finger and whose exit was on the palmar aspect of the same phalanx, was also observed with a compound, comminuted fracture of the proximal phalanx.

The wound was dressed with vaseline-soaked gauze, and a splint was applied. By July 11 the wounds had healed, and the fracture had united solidly, the finger was stiff, tender



FIGURE 8 Photograph of Both Feet of a Patient with Shell Fragment Wounds of the First and Second Toes of the Right Foot, Complicated by Obstinate Vasospastic Ischemia (Case 2). Note the moderate swelling, as well as the diffuse cyanosis contrasting with the finger-point blanching

and painful, however. The patient was sent to the physiotherapy section, where he received daily whirlpool-bath treatments and exercises for 2 weeks. On August 4 he was transferred to the rehabilitation group, where for 1 month he took part in the program but complained of pain and tenderness in the finger and that the whole hand became blue and cold, particularly when he was outdoors. Because of these complaints he was given further physiotherapy, with no improvement, and was returned to the hospital on September 4. Examination disclosed general pallor of the hand, with cyanosis (Fig 6). The radial pulse was palpable, but the ulnar pulse was not. A stellate ganglion block with novocain was done on September 6. This resulted in a warm, pink hand with palpable pulses that lasted for 3 days. Owing to a novocain reaction the block was not repeated, and on September 11 the finger scar was revised and a spicule of bone was removed in the hope of relieving pain. At the same time the ulnar artery was stripped just above the wrist. Good pulsations, surface color and temperature followed this

procedure, but after 1 week the signs and symptoms of local ischemia returned. By that time even the uninjured fingers had limited motion and the functional result was poor.

On September 28 an upper dorsal ganglionectomy was done through a posterior incision the second and third thoracic segments being removed. This resulted in a warm pink hand with good pulses (Fig. 7), and no further evidence of ischemia. Function of the hand was completely restored except for permanent stiffness of the proximal joint of the little finger.

Case 2. W. S., a 31 year-old private, was wounded in action in France on July 7, 1944 by fragments from an 88-mm. shell. He sustained wounds of the right upper arm, both buttocks and the first two toes of the right foot. On the same day the wounds were debrided and a metallic foreign body was removed from the second toe under Pentothal anesthesia at an evacuation hospital.

On July 13 the patient arrived at a general hospital in England where examination revealed a moderate penetrating wound on the posterior aspect of the right upper arm, moderate lacerating wounds of both buttocks, moderate penetrating wounds on the medial aspect of the right great toe and the lateral aspect of the right second toe, compound comminuted fractures of the middle and distal phalanges of the right first toe and middle phalanx of the second toe, and a metallic foreign body in the middle phalanx of the right second toe.

The wounds healed promptly without surgical closure. The patient was urged to get about but complained that pain in the great toe prevented his becoming ambulatory. On August 15 the ward surgeon insisted that he attempt to walk. When he did so the foot became swollen, cyanotic and cold. He complained of pain throughout the whole foot, particularly over the scar on the great toe. The dorsalis pedis pulse was palpable but weaker than that of the opposite foot. A course of physiotherapy was ordered with no improvement in 2 weeks. On September 1 a plastic repair was done on the scar of the first toe, and the foreign body was removed from the second toe. The scar subsequently gave no further pain, but the foot remained cold and cyanotic and he complained of pain through the foot (Fig. 8).

On September 13 a lumbar ganglion block was done with good immediate results. The color and surface temperature improved, and there was subjective relief that lasted for 4 days. On September 20 a second lumbar block afforded similar relief but for only for 1 day.

On September 28 a lumbar ganglionectomy was done, with sustained relief. Thereafter the foot remained warm, pink and painless. There was some swelling when the patient became ambulatory, but this subsided with use and the patient was walking well and without complaint when he was discharged from the hospital on November 2 (Fig. 9).

These cases, which are extreme rather than representative, are reported to illustrate the full range of therapy, of which lesser measures usually suffice. In most cases careful attention to supportive routine, in addition to several sympathetic blocks, restored adequate circulation. Often, a single novocain block brought about improvement that could be maintained by careful attention to the supportive measures mentioned above. The amount of treatment indicated depends entirely on the stubbornness of the vasospasm, which can be measured only by its response to therapy.

#### CIRCULATION

In a discussion of the treatment of vasospasm some consideration should be given to the objections to sympathetic paralysis recently presented by Cohen<sup>6,7</sup> and supported by the experiments of Friedländer et al.<sup>8</sup> Cohen points out that the circulation of the deep structures, particularly the muscle bellies, is independently regulated as compared with that of the surface structures, because

their needs for increased blood supply do not coincide. He concludes that an extremity with a blanched, cool surface represents a protective mechanism, the available blood being shunted to the deep structures, which are more vulnerable to its loss. He believes that sympathetic paralysis, under these conditions, diverts blood to the surface



FIGURE 9 Photograph of the Same Feet after Right Lumbar Ganglionectomy

Note the improvement in color and the absence of swelling

at the expense of the deep circulation and thus prevents the anticipated result.

These arguments, besides being of considerable interest, are of more than academic importance to anyone responsible for the care of this complication. Obviously, the treatment will be almost exactly reversed depending on which view is favored. These reports, which appeared while many of these patients were under treatment, afforded no comfort. In spite of a reevaluation of results with these arguments in mind it could be concluded only that extremities presenting varying degrees and extent of vasospasm were clinically improved by sympathetic paralysis. Not only were surface changes noted but also pulses improved, discomfort decreased and activity increased. The treatment was therefore continued, pending further study. The relation of the deep and surface circulations will stand further investigation, but a reversal of the treatment of vasospasm does not seem to be indicated.

Clinically, the indication for sympathetic paralysis is the presence of vasospasm — in fact,

block is a therapeutic test for the presence of vasospasm as distinguished from mechanical occlusion. If, in an ischemic extremity, one could be certain that the impairment was organic and fixed with no spasm of the collateral vessels, there would be no point in attempting to alter the distribution of this fixed supply. Clinical improvement following sympathetic block is believed to indicate the presence of vasospasm, and there is increasing evidence that it complicates peripheral injury and disease more frequently than has been appreciated.

### SUMMARY

Vasospasm of varying severity and obstinacy may complicate peripheral injuries, particularly those in which there is an element of concussion involving increased tissue tension.

Neither extensive injury nor involvement of nerves or blood vessels is necessary to the development of vasospasm.

Subjectively, there is local discomfort and resistance to function. Objectively, there is de-

creased surface temperature, blotchy cyanosis and diminished pulses.

A persisting, low-grade ischemia causes trophic changes that materially impair the functional result.

Two cases of traumatic arterial vasospasm in which sympathetic block resulted in clinical improvement are presented.

520 Commonwealth Avenue

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## VAGINAL SMEARS AS AN AID IN THE DIAGNOSIS OF EARLY CARCINOMA OF THE CERVIX\*

MAURICE FREMONT-SMITH, M.D.,† RUTH M. GRAHAM, B.S., AND JOE V. MEIGS, M.D.‡

BOSTON

OF the 17,000 annual deaths in the United States from uterine cancer the large majority are caused by carcinoma of the cervix. It has been stated that only 11 per cent of cervical cancers reach the surgeon in the early stage, and 60 per cent are completely inoperable when treatment is begun.<sup>1</sup> There is still an average delay of seven months from the onset of symptoms to the institution of treatment. Efforts to educate physicians and the public to the vital importance of immediate diagnosis and treatment at the onset of abnormal vaginal bleeding or discharge have been only partially successful. Moreover, even clinically early cases continue to show recurrence of the disease after operation or radiation.

It is possible that the entire concept of the life history of cervical cancer needs revision: that the so-called "early case" presenting a short history of bleeding or a minimal visible lesion is, in fact, already a moderately advanced or advanced cancer. It is possible that early cancer causes no symptoms and that diagnosis in the incipient stage would be followed in most cases by cure of the disease.

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This hypothesis is substantiated by two recent reports. In July, 1946, Pund and Auerbach<sup>2</sup> published a study of 1200 cases in which the cervix was removed by hysterectomy for conditions other than cancer. Preinvasive cancer was found to be present in 47 cases (3.9 per cent), in addition several cases of unsuspected invasive cancer were found. The presence of cancer was not recognized from the gross appearance of the cervix in a single case. Only one out of 4 patients had had abnormal bleeding. The average age of the 47 women showing preinvasive cancer was thirty-six and a half years, in contrast to a second group of 50 consecutive biopsies showing invasive cancer, in which the average age was forty-eight and a half years. TeLinde<sup>3</sup> found identical figures — a thirty-six-year average age for 11 cases of preinvasive as contrasted with an average age of forty-eight years for overt cervical cancer.

In September, 1946, Taylor and Guyer<sup>4</sup> reported a case in which a biopsy of the cervix, taken in 1938, had been misdiagnosed. One pathologist reported epithelioma, transitional type, but he was overruled by a second pathologist, who believed that the tissue was insufficient for diagnosis. No operation was done. The patient had been examined every six months for seven years without the detection of any abnormality of the cervix. In 1945 a proliferative nodular lesion was seen on the cervix, a biopsy from

which showed early squamous-cell carcinoma with invasion. Preparation of additional sections from the tissue obtained seven years previously showed not only that cancer had been present but that (as in TeLinde's cases) beginning invasion had occurred in certain areas. The patient had been harboring cancer of the cervix without symptoms and without clinical evidence of the disease for seven years, and the clinical diagnosis seven years later was still "early carcinoma." Taylor and Guyer refer to Stevenson's<sup>8</sup> cases, one developing "clinical cancer" eight and a half years and another showing microscopical invasion three years after previous biopsies had demonstrated noninvasive carcinoma of the cervix. Smith and Pemberton<sup>4</sup> found an interval of four to six years between the discovery of early

In 1941 Papanicolaou and Traut<sup>9</sup> described a new method for the diagnosis of uterine cancer. Technical details of this test are described in their publication, as well as in a previous paper from this laboratory.<sup>8</sup> In brief, a dry pipette with capillary opening and capped by a rubber suction bulb is inserted into the posterior vaginal fornix, the bulb is released, and the pipette withdrawn. Fluid so obtained is blown upon a glass slide, fixed while still wet in equal parts of ether and 95 per cent alcohol and later stained and examined for cancer cells. Criteria for the recognition of cancer cells are given in the two publications referred to above.

Papanicolaou,<sup>10</sup> in 1943, reported 7 cases of "intradermal" carcinoma of the cervix in which vaginal smears were positive for cancer. Ayre<sup>11</sup> described 19

TABLE 1 Pertinent Data in Cases of Cervical Carcinoma

CASE No.	AGE	SYMPTOMS	VAGINAL SMEAR	BIOPSY	PATHOLOGICAL DIAGNOSIS
1*	37				
2*	46	Occasional bleeding for 3 mo.	Positive	—	Carcinoma in situ
3*	48	Vaginal spotting for 1 wk.	Positive	Insufficient for diagnosis	Carcinoma in situ
4*	49	Spotting for 2 mo	Positive	Carcinoma in situ	Carcinoma in situ
5†	35	Spotting for 6 wk.	Positive	Chronic endocervicitis	Carcinoma in situ
6†	45	None	Positive	Chronic endocervicitis	Carcinoma in situ
7	71	None	Positive	—	Carcinoma in situ
8	42	Spotting	Positive	Carcinoma in situ	—
9	43	Postcoital spotting	Positive	1st — Insufficient for diagnosis	Carcinoma in situ
	63	Bleeding for 2 mo	Positive	2nd — carcinoma in situ	Carcinoma (3 in situ)
10	57	Spotting for 8 mo.	1st — unsatisfactory 2nd — positive	—	Carcinoma in situ
11	38	Precancerous lesion suspected by physician	Negative	Chronic endocervicitis	Carcinoma in situ
12	39	Staining for 10 days	Positive	Carcinoma in situ	Carcinoma in situ
13	38	Occasional spotting	Positive	No specimen obtainable	Carcinoma in situ
14	57	Increase in discharge for 3 months, no bleeding	Positive	Carcinoma in situ	—
15	49	Bleeding for 1 day	Positive	Chronic endocervicitis	Carcinoma in situ
16	42	None	Positive	Leukoplakia	Carcinoma in situ
17	31	Bleeding for 4 mo	Negative	Chronic endocervicitis	Carcinoma in situ

\*Previously reported by Meigs et al.<sup>12</sup>

†Previously reported by Meigs.<sup>14</sup>

lesions by biopsy and the development of clinical cancer.

Rubin<sup>7</sup> reports 2 cases of early squamous-cell carcinoma of the cervix. One patient was followed for seven years subsequent to a positive biopsy, with no symptom or sign referable to the malignant lesion. The other patient showed no clinical evidence of disease until five years after the original positive biopsy.

If there is a period of years before the appearance of symptoms during which cancer of the cervix is nevertheless present and capable of diagnosis by serial section of the excised cervix, there exists, if one could but make use of it, a critical period during which treatment should result in cure in all or in a high percentage of cases. Although such lesions are often detected by biopsy, a satisfactory biopsy specimen is difficult to obtain in early cases in which no suspicious area is visible or in which, as occurred twice in our series, the lesion is endocervical. The pathologist can report cancer only if an area containing cancer is provided him.

cases in which the interesting diagnosis of "pre-cancer" was made. Abnormal cells were found in the cervical secretions of these women. It is difficult to know whether these cases fall into the group discussed below. Hertig<sup>13</sup> reports 8 positive and 5 negative smears in 13 cases of cervical carcinoma in situ.

In 1945 Meigs et al.<sup>12</sup> reported 3 cases of cervical carcinoma in situ in which vaginal smears were positive. Meigs<sup>14</sup> reported from this laboratory 2 additional cases of preinvasive carcinoma of the cervix in which vaginal smears were positive. In the 12 cases of cervical carcinoma in situ reported below, vaginal smears were positive in 10.

In the total group of 17 cases, 14 patients gave a history of bleeding or discharge, and 3 were without symptoms — of these, 2 had positive vaginal smears (Table 1). Initial biopsies were positive in 4 cases, and in 2 the initial biopsy was reported "insufficient for diagnosis" — in 1 of these a second biopsy showed carcinoma in situ. The biopsy diagnosis was chronic cervicitis in 5 cases and leukoplakia in 1. No biopsy

was performed in 4 cases, and in another no biopsy specimen could be obtained. Thus, in 8 of 12 cases, the initial biopsy failed to disclose the presence of carcinoma in situ, whereas of 17 cases examined by vaginal smear, this test was positive in 15\*.

The following are brief abstracts of the last 12 cases

**CASE 6** H P (private case), a 71-year-old woman whose cervix had been repaired in 1920, had been given radium for flowing in 1923. There had been no hot flashes or other symptoms. Examination disclosed scarring of the cervix. Biopsy revealed no suspicious area. Vaginal smears on February 12 and June 4, 1945, were positive. A hysterectomy was performed on July 24 and at the midpoint in the cervical canal a polyp, 0.5 by 0.3 cm in diameter, was found. The pathological diagnosis was epidermoid carcinoma in situ.

**CASE 7** S D (MGH 503466), a 42-year-old woman, complained of spotting preceding her periods. Examination disclosed an area of erosion about the os, with some bleeding at the lower margin. No suspicious area was seen. A vaginal smear was positive. The pathological diagnosis on a biopsy specimen was epidermoid carcinoma in situ.

**CASE 8** R B (MGH 547504), a 43-year-old woman, had had a supracervical hysterectomy for menorrhagia of 2 years' duration  $5\frac{1}{2}$  months previously. She complained of severe hot flashes. Vaginal spotting followed coitus  $1\frac{1}{2}$  months after operation. A vaginal smear was positive. No biopsy was performed. The pathological diagnosis was epidermoid cervical carcinoma in situ.

**CASE 9** S S (MGH 502116), a 63-year-old woman, had reached the menopause 15 years before admission. She had had no hot flashes. Bleeding for 1 day had occurred in June, 1945, and for 3 days in July. At biopsy on August 31 the tissue was insufficient for diagnosis, in another one, taken on September 7, the pathological diagnosis was epidermoid carcinoma of the cervix in situ. A vaginal smear on September 9 was positive. The final pathological diagnosis was epidermoid cervical carcinoma (? in situ).

**CASE 10** A H (MGH 519079), a 57-year-old woman who had reached the menopause 4 years previously, complained of occasional vaginal spotting of 8 months' duration until a curettage in another hospital 1 month before admission. A vaginal smear in January, 1946, was unsatisfactory, a smear on February 5 was positive. The cervix appeared normal. No biopsy was performed. The final pathological diagnosis was epidermoid cervical carcinoma in situ.

**CASE 11** A R (MGH 457627), a 38-year-old woman, had been informed of a precancerous lesion of the cervix by an Army medical officer on June 20, 1944. For 10 years she had noticed bleeding and pain after intercourse. A vaginal smear on August 5 was negative. A biopsy on August 7 revealed chronic endocervicitis. The pathological diagnosis on the excised uterus was epidermoid cervical carcinoma in situ.

**CASE 12** M D (private case), a 39-year-old woman, complained of staining for 10 days. Biopsies on September 28 and October 6, 1944, revealed carcinoma in situ. A vaginal smear on October 24 was positive. The pathological diagnosis was squamous-cell cervical carcinoma in situ (? early invasion).

**CASE 13** K W (private case), a 38-year-old woman, had had regular periods but intermenstrual bleeding for 3 months. The cervix showed a small area of leukoplakia. No tissue was obtainable for biopsy. A vaginal smear on November 12, 1946, was positive. The pathological diagnosis was epidermoid cervical carcinoma in situ.

\*A slide in another case was sent to this laboratory from the Free Hospital for Women. The smear was thought to be negative, although a pathological diagnosis of cervical carcinoma in situ had been made.

†Reported through the courtesy of Dr. Paul A. Younge.

**CASE 14** K T (MGH 130139), a 57-year-old woman, complained of an increase in vaginal discharge of 3 months' duration. There had been no blood. The cervix appeared normal to inspection. A vaginal smear on February 24, 1947, was positive. Biopsy on March 21 disclosed epidermoid carcinoma in situ.

**CASE 15** H V (private case), a 49-year-old woman with no symptoms, after 3 months of treatment with estrogens for arthralgia noted 1 day of spotting. A vaginal smear on November 27, 1946, was positive. Biopsy on December 16 revealed chronic cervicitis. The pathological diagnosis was carcinoma in situ.

**CASE 16** P F (MGH 545101), a 42-year-old woman, was admitted for a mass in the breast that proved to be due to chronic cystic mastitis. There were no pelvic symptoms. Examination showed an area of leukoplakia on the cervix. Vaginal smears on December 10, 12 and 21, 1946, were positive. Biopsy on December 14 disclosed leukoplakia. The pathological diagnosis on the excised uterus was cervical carcinoma in situ.

**CASE 17** D T (private case), a 31-year-old woman, had had continuous flowing for 4 months. There was a rough area on the left lip. A vaginal smear was negative. Biopsy revealed chronic cervicitis. The pathological diagnosis was cervical carcinoma in situ.

## SUMMARY AND CONCLUSIONS

Twelve cases of early cervical carcinoma are reported in which the vaginal smears were positive for tumor cells in 10. Two of these patients had had no symptoms referable to the lesion. In 9 cases in which biopsy was performed, a diagnosis of cancer on the initial specimen was made in only 3.

Preinvasive carcinoma exists for several years before clinical evidence of the disease appears. When a carcinomatous lesion of the cervix manifests itself by symptoms it is often no longer in the early stage. Early diagnosis is essential if cancer of the cervix is to be cured. Diagnosis of preinvasive carcinoma of the cervix is possible by study of the vaginal smear.

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## AN OUTBREAK OF SMALLPOX IN AMERICAN MILITARY PERSONNEL IN JAPAN

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**SMALLPOX**, an ancient disease whose prevention has been so readily achieved since the days of Jenner, continues to manifest itself. Even in some parts of the United States the record is shameful. A number of states, especially in the West and Northwest, do not have compulsory vaccination laws. In 1924 Minneapolis had 860 cases, with 219 deaths. In 1931 a total of 30,232 cases were reported from the country as a whole. More recently, however, the morbidity figures have markedly declined, there having been reported only 346 cases in this country in 1945.

Most physicians have never seen a case of smallpox, particularly those who practice in states in which vaccination laws are rigidly enforced. Furthermore, the majority of cases that have been described in this country in recent years have been relatively mild. On the other hand, North Africa and the Far East, especially India, are hotbeds of hemorrhagic smallpox.

Unquestionably, the health of the armed forces during the recent conflict was the best ever on record. The program of preventive medicine as outlined and carried out was generally quite adequate. Consequently, an outbreak of smallpox among American troops stationed in Japan came as a surprise and as a rude jolt.

Smallpox, an acute infectious disease of virus etiology, is highly contagious and is transmitted from man to man and by fomites. Standard textbooks present a full discussion of the etiology, incidence, pathology and diagnosis. The case reports presented below, however, will serve to clarify, illustrate and amplify virtually all aspects of the disease.

During January, 1946, a total of 17 patients with smallpox were admitted to a station hospital. I was ordered to this institution at the time of the peak of the outbreak to lend assistance. Since this afforded a rare opportunity, a detailed report of these cases is considered justifiable.

## CASE REPORTS

**CASE 1** This man was on duty in December 1945 in a Japanese town. In his duties which consisted of guarding and inspecting a Korean repatriation area, he came in contact with countless natives. Several cases of smallpox among civilians had recently occurred. On December 17 the patient was admitted to a medical battalion clearing station because of complaints later shown to have been the prodrome of smallpox. On December 19 a rash broke out. Several days later the diagnosis of smallpox was made. The course was stormy but the patient began to improve, and on January 12, 1946, he was transferred to a station hospital for convalescence.

At that time, he was almost entirely free from crusts. The patient stated that he had been vaccinated in childhood but he recalled no definite "take," nor did he remember having had a scar on either arm. A vaccination in August, 1944 while he was in the Army, did not appear to have been successful.

**CASE 2.** This man was in the same ward in the medical battalion clearing station as the patient in Case 1. He had a cellulitis of the left ankle at the time of that patient's admission. On December 29 he was vaccinated. On the next day he began to develop symptoms that eventually showed themselves to have been the prodrome of smallpox. On January 2 he was transferred to the station hospital without a definite diagnosis. A reaction to the vaccination was suspected. The patient, however, was isolated on the fourth floor of the hospital. Medical aseptic technic was said to have been employed. On January 6 the diagnosis of smallpox was made. Two days later the patient expired of hemorrhagic smallpox. The vaccination on entrance into the Army was reported to have been "immune." A childhood vaccination had not been successful.

**CASE 3** This man was one of a series of patient contacts in the station hospital. (There was no history of any direct contact with the patient in Case 1 who had been isolated, but epidemiologically speaking there is no other plausible explanation for these cases.) He was admitted to the station hospital on December 2 with the diagnosis of infectious hepatitis. He was placed in the hepatitis ward on the fourth floor. On January 14 he developed symptoms that were later shown to have been the prodrome of smallpox. Three days later a rash appeared. The patient was isolated. He ran a typical course of severe pustular smallpox, from which he convalesced slowly. He recalled a childhood vaccination but could not remember whether it had been successful. In July, 1944 a vaccination done in the Army had apparently been unsuccessful.

**CASE 4** On December 30 this patient was admitted to the third floor of the station hospital with the diagnosis of malaria. He received routine antimalarial therapy, and on January 8 he was returned to duty. Six days later he developed prodromal symptoms of smallpox. On January 16 he was readmitted to the hospital. He was again placed on the third floor. He developed a rash on January 18 and expired from hemorrhagic smallpox on January 23. A vaccination on November 28, 1944 had been reported as "immune." A childhood vaccination at the age of 7 years was said to have been successful.

**Autopsy.** Post mortem examination disclosed the shotty, hemorrhagic, umbilicated vesicles covering most of body confluent on the face, chest, abdomen and proximal portion of the extremities. The lungs showed congestion, edema and hemorrhage in all lobes. There was acute, hemorrhagic tracheobronchitis. Petechial hemorrhages over all the pleural surfaces were observed. Petechiae were scattered over the pericardium and endocardium. There was mild endocarditis. The gastrointestinal tract showed petechial hemorrhages and superficial erosions of the esophagus, stomach and the small and large intestines. A moderate hepatomegaly with diffuse fatty changes in the middle and central zones, was observed. The genitourinary system revealed chronic interstitial nephritis, bilateral with massive hemorrhagic hemorrhage into the renal pelvis congestion and cloudy swelling. There was bilateral ureteral congestion and hemorrhage as well as blood clots in both ureters and in the bladder. There were petechial hemorrhages of the bladder mucosa. Acute orchitis with interstitial congestion and hemorrhage was noted. Petechial hemorrhages were observed over the tunica vaginalis. There was a moderate splenomegaly.

**CASE 5** On January 4 this man was admitted to the third floor of the station hospital with a diagnosis of malaria.

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became worse, and blood-streaked sputum was seen. Numerous small gray ulcerations were observed in the tonsillar fossa at that time. Hematuria set in but was of a lesser degree than that in the other hemorrhagic cases. The cough became worse, the condition became critical, and the patient expired rather suddenly. There was no characteristic fall in temperature at the time of the onset of the rash.

*Purpura variolosa*. Eight of the fatal cases were of the purpura-variola type. After the prodromal period, these patients uniformly presented a scarlatiniform flushing of the face, neck and chest. The extremities showed a mottled, reddish appearance. Subconjunctival hemorrhages were seen early. About thirty-six to forty-eight hours later the patients exhibited a purpuric eruption that was more or less generalized, not marked on the face but especially prominent on the chest, forearms, feet and legs. At about that time the face and extremities (especially the arms) became edematous, the eyelids swelled, and the conjunctivas were markedly hemorrhagic. Large quantities of thick mucus streaked with blood were raised, cough was marked, and efforts to swallow were frequently unsuccessful. Drooling occurred. The voice was thick and weak. Enemas yielded returns of bloody water. The sites of injections bled for minutes to hours. After several days vesicles formed, especially on the chest, with a few on the extremities. Some of the vesicles were hemorrhagic.

Three patients took on a slate-gray appearance. Four had small, closely spaced vesicles over the chest and extremities.

All fatal cases exhibited coarse, moist rales and rhonchi in the chest. The patients became extremely toxic. Large blebs on the wrists and ankles were noted prior to exitus in 4 cases. Two patients never developed much of an eruption, except for the slate-gray hemorrhagic appearance.

As the exitus approached, the patients became extremely stuporous. Respirations were somewhat labored, and coarse, moist rales were audible even without the use of a stethoscope. The impression was obtained that the patients were overwhelmed by the infection.

#### THE THERAPY

##### *Hemorrhagic Cases*

It is at once apparent that there is still no satisfactory therapy for the hemorrhagic cases. The mortality is virtually 100 per cent. In this series there were no recoveries. All the patients in this group received penicillin therapy. At first, the dose was 20,000 units intramuscularly every three hours. Later, this was increased to 40,000 units a dose. There was no tangible effect from the penicillin therapy. Daily blood transfusions were given in amounts of 150 cc daily. The fluid intake was largely handled by the intravenous route, since the oral intake in these cases was greatly restricted owing to difficulty in swallowing. Each day, 2000 cc

of 5 per cent glucose in physiologic saline solution or 10 per cent glucose in distilled water was given. Plasma was administered in amounts of 250 cc daily.

Adrenocortical extract was also given to 5 patients. No visible benefits were seen. Vitamins K and C were also administered, the intravenous route being utilized for the most part. The first patient to convalesce was employed as a donor for the other serious cases. Ten cubic centimeters of his whole blood was given twice to 5 of the seriously ill patients. This amount was no doubt inadequate.

Locally, various preparations were used. Petroleumatum, sodium bicarbonate and plain calamine lotion were tried. It was difficult to furnish relief. All the patients complained that the light hurt their eyes, and a darkened room afforded them much relief. A 10 per cent solution of mild silver proteinate was instilled into the eyes several times a day.

Aspiration, oral hygiene, sedation and oxygen therapy were employed on indication. It is obvious that none of these measures were helpful in preventing the final outcome of the disease. In these cases, despite modern science, one stands by helplessly at the sick bed. The situation is characteristic of that in many virus diseases: once the cells have been invaded, therapy is generally of no avail.

##### *Pustular Cases*

In these cases the advent of penicillin represents a therapeutic advance. Although it is difficult to draw definite conclusions from the cases presented above, the employment of penicillin is certainly logical. The pustular stage should indeed be favorably influenced by this antibiotic. Blood transfusions and parenteral therapy were given when needed, as were local applications and other palliative and supportive measures.

##### *Mild Cases*

The treatment in these cases was minimal. One patient received penicillin therapy for three days.

#### DISCUSSION

In the study of these cases there were a number of interesting factors for consideration. Unfortunately, a post-mortem examination was possible in only 1 case. Facilities for autopsy were poor, and in view of the highly contagious nature of the disease, it was considered prudent to minimize exposure. It must be pointed out that at the time of the outbreak the situation about the institution was one of some understandable uneasiness. The wide variety of the contacts instilled a wholesome awe for the ease with which the disease could be spread and even some doubt concerning the efficacy of vaccination. Fortunately, the value of smallpox vaccination was again demonstrated beyond doubt. Many of the unvaccinated patients had come from states where compulsory vaccination laws exist. In the 3 mild cases clear-cut histories of childhood

vaccination were obtained. Two patients still showed a scar. A vaccinoid reaction within a three-year period prior to the attack was recorded in 2 cases.

In the severe, pustular cases, the history revealed either an unsuccessful childhood vaccination or none at all. Vaccinations done within a three-year period were recorded as "immune" reactions in 3 cases. In another case no record was available.

In only 1 of the fatal cases was there a fairly reliable history of a successful childhood vaccination. Four patients apparently had received no childhood vaccination, and the remaining 5 provided an unreliable history. The severe eruption made identification of any old scars impossible. In 8 of the fatal cases the patient had had an "immune" reaction within three years of the illness. In 1 case the reaction was reported as "vaccinoid," and in another the immunization register was unobtainable.

Despite the incompleteness of some of the vaccination data, however, certain points stand out. Vaccination is not so universal in the United States as one might think. Even in states with compulsory vaccination laws there seem to be many slips. It seems to be fairly well established that vaccination in the armed forces has not always been performed with sufficient care—especially regarding the recording of reactions. Interrogation of some of the patients caused doubt whether they had ever received successful vaccinations in their lives. There had at times been a tendency to fail to read and to interpret the vaccination properly. It seems quite certain that many "immune reactions" should have been recorded as "no take."

In addition, it is apparent that even successful vaccination does not necessarily confer lifelong immunity. A successful childhood vaccination, however, frequently prevents the attack from becoming hemorrhagic. Whenever an area in which cases of smallpox have occurred is entered, all persons should be vaccinated without delay.

The universal revaccination of all troops and personnel, the enforcement of a working quarantine on the hospital and the strict isolation of all cases, contacts and suspects quickly terminated this outbreak.

The high degree of contagion of smallpox is again demonstrated. All but 3 of the cases were definitely related to Case 1. This fact, however, indicates that the contact need only be fleeting. Presumably, the effectiveness of the isolation technic used at the station hospital was average, although breaks obviously occurred. On the other hand, there seems

to be no reason to assume that smallpox is spread in a mysterious way by winds blowing from "pest houses" and the like. Medical aseptic technic employed by an adequately vaccinated personnel, with the patient completely isolated, should afford adequate protection. It is gratifying and reassuring to note that none of the physicians, nurses or attendants in intimate contact with these patients contracted the disease. Such persons were promptly revaccinated.

Until the fact of an epidemic has been established, the diagnosis of a case early in the disease is frequently difficult. This applies especially to the hemorrhagic cases, with their early scarlatiniform flush. Many of the cases also resembled measles. The mild cases naturally bring up the question of chicken pox. The long prodromal period is of help in suggesting the possibility of smallpox.

Apparently, hemorrhagic smallpox is merely a severe form of the disease. There seems to be no validity in postulating a hemorrhagic strain of the virus, since all varieties of smallpox originated from the same source. It is probable that the degree of exposure and the extent of the immunity had a bearing on this matter.

The incubation period in these cases averaged about two weeks, which is in harmony with the usual experience. The time can be less than that period, however, and also of greater duration.

#### SUMMARY

An outbreak of 17 cases of smallpox, with 10 deaths, is reported and discussed.

Hemorrhagic cases are highly fatal, representing a 100 per cent mortality in this series.

Penicillin therapy is of promise in cases of the pustular variety.

The high degree of contagion of smallpox is again demonstrated.

The difficulty of early diagnosis is emphasized, especially among the first cases of an outbreak.

Vaccination is still the only satisfactory answer to the problem. A scrutiny of the vaccination history in these cases showed that the protection had been inadequate for the most part.

In the face of actual cases, the entire personnel must be revaccinated.

Fresh vaccine, proper vaccinating technic and the correct interpretation of the reactions are essential to an effective program of prevention.

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## HEMOGLOBINEMIA ACCOMPANYING TRANSURETHRAL RESECTION OF THE PROSTATE\*

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THE removal of the prostate by the transurethral method, together with newer methods of preoperative and postoperative care of the patient by the use of fluid therapy and antibiotics, has increased the number of patients who may safely be subjected to prostatectomy. In spite of the present refinements, transurethral resection carries an appreciable — although low — mortality. One of the disturbing complications sometimes noted is a temporary oliguria or even anuria. A fatal case of renal failure following transurethral prostatectomy called attention to the possibility that intravascular hemolysis played a part in its causation. The following is a brief abstract of this case.

A 62-year-old salesman was admitted to the hospital on July 5, 1945, because of inability to urinate of 12 hours' duration. He gave a history of increasing prostatism during the preceding year.

Physical examination was negative except for a blood pressure of 200/110 and a markedly distended bladder. The prostate was enlarged about twice the normal size on rectal examination, but showed no evidence of cancer.

Examination of the blood revealed a hemoglobin of 9 gm per 100 cc and a white-cell count of 9800, with a normal differential count. The urine, which showed a specific gravity that ranged between 1.006 and 1.012, gave a +++ test for protein, the sediment contained an occasional red and white cell. The blood urea nitrogen was 8 mg per 100 cc, and the phenolsulfonephthalein test showed 39 per cent excretion of the dye in 30 minutes and 65 per cent at the end of 2 hours.

After catheterization the patient was able to void spontaneously, and on the 4th hospital day a transurethral prostatectomy was performed under combined spinal and Pentothal anesthesia. A moderate amount of bleeding occurred during the resection, and a transfusion of 500 cc. of citrated blood, found on crossmatching to be compatible, was given while the operation was in progress. This was followed after operation by 1000 cc of distilled water containing 5 per cent dextrose, and later a second transfusion of 500 cc. of citrated blood was given because of continued bleeding and a low blood pressure. A sample of serum obtained before the second transfusion, for the purpose of crossmatching, was observed to show marked hemolysis.

On the 1st postoperative day the patient appeared ill, he was restless and nauseated, and the urinary output was low. Bleeding was slight. The blood urea nitrogen was 65 mg per 100 cc. In the afternoon the blood serum showed a hemochromogen level§ of 199 mg and a total bilirubin of 2.08 mg per 100 cc. On the 2nd day the hemochromogen level was 130 mg and total bilirubin 0.77 mg per 100 cc, and 3 days later the hemochromogen level was 33 mg per 100 cc.

Throughout the 1st postoperative week the patient produced only a small amount of urine, the total output being

about 1500 cc. The blood urea nitrogen rose to 90 mg per 100 cc on the 3rd and to 120 mg on the 5th postoperative day. During that time the patient received supportive therapy, which included intravenous fluids, whole blood, plasma and amino acids, since he was unable to take anything by mouth. On the 8th day a diuresis of 1400 cc occurred. Thereafter, the patient maintained an output of over 2000 cc. of urine daily, but the specific gravity was persistently low, and the urea concentration of the urine varied between only 121 mg and 285 mg per 100 cc. (normal 2500 to 3000 mg). This, with blood urea nitrogen levels between 110 and 140 mg per 100 cc, demonstrated an almost complete lack of concentrating power on the part of the kidneys. On the 11th postoperative day the patient developed auricular fibrillation, dying on the next day of cardiac failure. Permission for autopsy was not obtained.

It seemed evident that in this case intravascular hemolysis, as demonstrated by an elevated serum hemochromogen level, was followed by hemoglobinuric nephrosis. An intrinsic hemolytic anemia seemed an unlikely cause for this reaction, since all laboratory tests, including cold hemolysis, acid hemolysis, hypotonic fragility, sickling preparation and cold agglutination, were within normal limits. The two transfusions of bank blood that the patient received had been rechecked for type and compatibility, and both were found to be compatible. One was Type O and Rh positive, and the other Type O and Rh negative, the patient was Type O and Rh positive. The small dose of sulfadiazine — 1 gm daily for four days — given preoperatively in the absence of other evidence of sensitivity, spherocytosis or abnormal agglutination did not account for the severe hemolytic reaction.

It was suggested that the operation of transurethral prostatectomy in itself was responsible for the hemolysis. Accordingly, the blood of 15 consecutive patients undergoing transurethral resection was tested for the presence of hemolysis¶ by measurement of the serum hemochromogen level before and immediately at the close of the procedure (Table 1). All patients were operated on by the technic described by Nesbit.<sup>2</sup> A Bovie generator was used, and distilled water for irrigation was obtained from a reservoir about 75 cm above the level of the bladder.

In this group 10 patients (66 per cent) showed significant hemolysis, the blood hemochromogen levels after operation ranging between 24 and 316 mg per 100 cc. In 3 cases the level was over 200 mg per 100 cc — that is, within the range observed in the patient with renal failure described above.

¶This suggestion was made by Dr. Joseph Ross.

§A sample of blood was drawn from an antecubital vein, allowed to clot and centrifuged, and the supernatant serum separated within thirty minutes. All transfers of blood were made under mineral oil. Hemochromogen levels were determined by the method of Flink and Watson.<sup>1</sup>

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§The blood hemochromogen level is a measure of all pyro iron pigments free in the blood stream, including not only hemoglobin but also methemoglobin, hematin and methemalbumin. The principal substance found free in the blood stream immediately after hemolysis has taken place is hemoglobin, but if determinations are made a number of hours later appreciable amounts of the other substances may also be found. These other substances are derived from the free hemoglobin originally present. The hemochromogen levels mentioned below are therefore a measure of the amount of hemolysis that had taken place.

All but one of the patients showing hemolysis made a good recovery and gave no evidence during this period of any renal damage or increased nitrogen retention as a result of the operation with its attendant hemolysis. One patient, however, with

second day, which returned slowly to normal after ten days.

At least two possibilities are suggested as the cause of the observed hemolysis: local action of the electric energy of the instrument on blood-contain-

TABLE 1 Hemochromogen Levels before and after Transurethral Resection of the Prostate

PATIENT	AGE	DIAGNOSIS	DURATION OF OPERATION	TISSUE REMOVED	TRANSFUSION*	SERUM HEMOCHROMOGEN LEVEL	
						BEFORE OPERATION	AFTER OPERATION
	yr		min	gm	cc	mg /100 cc	mg /100 cc
W. A.	65	Benign prostatic hypertrophy	50	10	—	4	11
C. T.	42	Benign prostatic hypertrophy	75	—	300	1	31
S. W.	59	Benign prostatic hypertrophy	60	79	—	—	52
B. B.	66	Benign prostatic hypertrophy	40	4	—	—	13
H. H.	72	Carcinoma of prostate	35	2	—	—	52
G. B.	63	Benign prostatic hypertrophy	60	12	—	2	265
C. F.	68	Carcinoma of prostate	35	16	—	—	2
C. G.	68	Benign prostatic hypertrophy	35	6	—	4	32
R. M.	59	Benign prostatic hypertrophy	120	18	—	—	24
J. R.	73	Benign prostatic hypertrophy	75	10	—	7	110
K.†	65	Benign prostatic hypertrophy	35	19	500	—	220
J. P.	71	Benign prostatic hypertrophy	50	10	—	—	65
S. McP.	77	Carcinoma of prostate	60	16	—	4	6
J. B.	64	Carcinoma of prostate	0	13	500	—	316
W. L.	70	Benign prostatic hypertrophy	85	—	—	8	12

\*Blood given after hemochromogen determination

†Patient had oliguria for one day

a hemochromogen level of 220 mg per 100 cc, had temporary oliguria on the day after operation, despite an adequate fluid intake (3200 cc). This lasted for only about twelve hours, during which almost no urine was formed, and was followed by

ing tissues, and the penetration of the irrigating fluid (distilled water) into the blood stream either by lymphatic absorption or into venous channels opened by operation, with resulting hemolysis.

The first possibility seemed remote, in view of the absence of hemolysis in patients subjected to fulguration of bladder papillomas by the same type of electric current as that used in the resectoscope.

To investigate the possibility that distilled water used for irrigation during the resection gained access

TABLE 2 Hemolytic Effect of Water Administered Intravenously in Man

AMOUNT OF WATER INJECTED	SERUM HEMOCHROMOGEN LEVEL AFTER INJECTION
cc	mg /100 cc
100	11
200	21
300	45
400	47
500	70*
900	360*

\*Hemoglobinuria present.

to the blood stream, sodium salicylate, in amounts of 1 gm per liter, was added. This substance was chosen to label the irrigating fluid, since a method of accurately determining its presence in small amounts in the blood has been described by Brodie et al.<sup>2</sup> Also, it was found that in this concentration in the irrigating fluid, sodium salicylate caused no interference with the cutting action of the resectoscope. The blood levels of sodium salicylate to be expected an hour after the administration of varying amounts of this drug were investigated in several patients prior to its use in transurethral prostatectomy (Fig. 1).

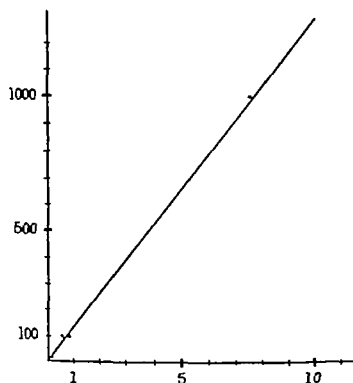


FIGURE 1 Sodium Salicylate Blood Levels following the Intravenous Injection of the Drug

The ordinate represents the amount of drug injected (in milligrams) and the abscissa the blood level (in milligrams per 100 cc) one hour after injection.

a diuresis lasting for two days with an output of over 2000 cc on each day. The damage to the kidneys was reflected by a postoperative rise in the blood urea nitrogen to 53 mg per 100 cc on the

Three patients were subjected to transurethral prostatectomy, an irrigating fluid containing 1 gm of sodium salicylate in 1000 cc of distilled water being used. In 2 cases no sodium salicylate could be demonstrated in the blood, nor was there any hemolysis. The third patient, in whom a large amount of hemolysis occurred, — a hemochromogen level of 316 mg per 100 cc, — also showed the presence of sodium salicylate, the blood hemochromogen level at the end of operation being 7.5 mg per 100 cc. This level of sodium salicylate is to be expected an hour after the intravenous administration of about 1 gm of this substance and therefore represents the entrance of about 1000 cc of irrigating solution into the blood stream.

In the patients studied it has been assumed that the distilled water entering the circulation caused hemolysis of the blood. Such a fluid is well known to be hemolytic for red cells in vitro. Krumbhaar,<sup>4</sup> in experiments on dogs, found that the intravenous injection of distilled water of 2 to 3 per cent of the body weight produced hemoglobinemia and hemoglobinuria, and that the speed of injection — from three to forty-five minutes — had little effect on the amount of hemolysis. To check the validity of these data for man, distilled water was given intravenously in amounts from 100 to 900 cc to several patients. The smaller amounts were given rapidly over one or two minutes. The larger amounts (300 to 900 cc) were given slowly over a period of one to four hours. Appreciable hemolysis was produced in every case (Table 2). In no case was there any reaction or evidence of renal dysfunction after injection. The data suggest that amounts of distilled water in the neighborhood of 500 cc or more are necessary to produce hemoglobinuria.

### DISCUSSION

Intravascular hemolysis is a frequent consequence of transurethral prostatectomy. Evidence has been presented that distilled water used for irrigation gains access to the blood stream and that it is capable of producing the degree of hemolysis observed. The demonstration by Nesbit of free venous bleeding from veins of the prostatic capsule injured during operation makes it quite evident that these are a portal of entry for the fluid, when its pressure exceeds that in the veins. Although the fluid used for irrigation already contains hemolyzed blood, this accounts for only a fraction of the hemolysis observed.

There is no reason to believe that the renal damage resulting from hemolysis during transurethral resection differs essentially from other types of hemoglobinuric nephrosis. The pathogenesis of the renal failure in these conditions is not yet well understood, as pointed out by Bradley.<sup>5</sup> Hemoglobinemia

is not the sole cause, for comparable hemolysis has been produced<sup>6</sup> and comparable amounts of distilled water have been injected intravenously<sup>7</sup> without causing renal damage. Probably, blood loss and renal ischemia<sup>8, 9</sup> both of which may well occur during transurethral resection, play an important contributory role in the pathogenesis of the renal lesion.

Regarding the prevention of such hemolysis, in view of the possibility that fluid enters the circulation through venous channels opened during operation, the use of irrigating fluid under as low a pressure as possible and in as small a quantity as is consistent with clear vision is self-evident. The employment of a fluid such as physiologic saline solution, which is well borne in the general blood stream, is precluded because the cutting current of the resectoscope cannot be efficiently produced in a medium containing strong electrolytes. The addition of some nonelectrolyte, such as glucose, to the irrigating fluid has been tried but has not been found entirely satisfactory because of impaired vision.

### SUMMARY

A fatal case of renal failure following transurethral prostatectomy is described. Death was caused by massive intravascular hemolysis occurring during the operation.

Fifteen patients undergoing transurethral prostatectomy were studied for the presence of hemolysis, by measurement of the serum hemochromogen level immediately at the termination of operation. In 10 cases a significant amount of hemolysis could be demonstrated, with extremely high hemochromogen levels in 3 cases, resulting in temporary oliguria in 1 patient.

Evidence is presented that this hemolysis is caused by the entrance of distilled water into the blood stream through venous channels opened during operation.

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## MEDICAL PROGRESS

## INDUSTRIAL MEDICINE

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INDUSTRIAL medicine in the first postwar year continued to show the influence of the lessons learned from the war. New ideas, new methods, new procedures and new viewpoints that originated in war experiences were encountered everywhere. The progress made may be divided into two groups, technical and social.

Technical advances were manifold and should prove of enduring value. General safety programs in many war industries reached a new high level, with gratifying results. In the munitions industry lessons learned from World War I were remembered and utilized, new experiences were added, and safety devices introduced that proved highly effective. As a result fatalities among munition workers during the war were remarkably small compared with the records of 1918. Industrial hygiene also profited from experiences in dealing with the hazards of radioactive substances of all kinds. The most dramatic achievement during the war — the liberation of atomic energy — has brought with it, and will continue to do so, new hazards to personnel employed in plants where this new force is generated. Safeguards have, on the whole, been unusually effective, and thanks to the war and the preproduction research, industrial hygiene has known methods to protect employees from dangerous exposures.

The social advances proved even greater than those won in the technical field. Experience has taught that mechanical safety devices by themselves are not sufficient to achieve the best results. The human element has also to be considered, and the co-operation of the group and the individual worker enlisted. Thus, a new concept has developed that of the worker as a "total man" whose mental and emotional traits and responses are as important for high productivity as his physical capabilities. Since these emotional responses depend not only on working environment but also on conditions outside the working place, another social development followed logically. Plant services were integrated with community health programs, and preventive medicine has become an important factor in ensuring not only the well-being and happiness of the worker but also an increase in his productivity. Management and labor alike are recognizing more and more the necessity and the value of industrial medical services. During 1946 a constantly growing co-operation of employer and employee in instituting

and maintaining an effective in-plant medical department has led to encouraging results. Also, workmen's compensation laws show a growing trend toward liberalization, and the "subsequent injury" law already adopted by thirty-two states is a progressive step in this direction, this law relieves the insurance carrier and the employer from being excessively liable when employing a handicapped worker, veteran or nonveteran.

In the educational field, industrial medicine has likewise made valuable advances. Many colleges and universities have recognized this branch of medical science and have instituted special courses to train competent industrial physicians and engineers. The need for providing medical services for the smaller plant has been appreciated, and numerous plans have been suggested by industrial physicians and agencies interested in the field of industrial medicine. One index of the general progress made in the field of industrial medicine is the increased employment of industrial nurses. In 1941 only 6000 nurses were doing industrial work, whereas in 1945 their number had risen to 14,000 — an increase of 133 per cent.

## ATOMIC ENERGY AND PHYSICAL AGENTS

The fact that atomic power has been harnessed on an industrial scale for the first time in history brings the possibility of the more widespread industrial uses of atomic energy appreciably nearer and makes it of immediate importance to the industrial physician, who will have to face the new and difficult problems posed by nuclear energy. Bale<sup>1</sup> points out that until recently nuclear energy was produced only in large-scale operations at fixed sites where adequate methods of protection reduced to practically nothing the hazards to personnel. Health reports from Oak Ridge, for example, were uniformly good, and Clarke<sup>2</sup> states that the anxiety that working with radioactive materials might cause sterility is completely refuted by the birth rate at Oak Ridge, which was one of the highest of any city in the country. All these protective measures, however, have been expensive and have required the continued vigilance of the staff charged with the safety of the project.

Atomic energy will presumably be used in industry in nonmobile plants as a source of electricity, and as such it will have to compete economically with electricity derived from water power and from coal-burning installations. Despite the economic

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necessity of cutting costs, the industrial physician and engineer charged with the health and safety of workers, as well as with the health and safety of inhabitants living in the neighborhood of nuclear plants, must insist on adequate protection and safety measures, even if the needed precautions may have to be more elaborate than ordinarily realized

Dowdy<sup>3</sup> offers the reassurance that no insuperable difficulties stand in the way of adequate protection of workers and public alike, for the types of radiation encountered in the liberation of atomic energy are in the main not new either to physicians or to radiologists and physicists. The radium industry has for many years dealt with and overcome these problems. Only neutron radiation is a completely new type of radiant energy not previously encountered in industry. The enviable record of the Manhattan District Project, however, is ample proof that the hazards of production in this field need be no greater than those in many other industries.

Kennedy<sup>4</sup> likewise states that although the high level of neutron and gamma radiations of nuclear matter represents a real hazard to operators, observers and bystanders and although these hazards, being inherent in the fission reaction, are not subject to elimination from the process, they are definitely subject to careful control.

In the extensive wartime industry of radium dial painting, in which workers were inevitably exposed to radium, work has been done to prevent the fatal anemias and osteosarcomas that claimed many victims after World War I. In a discussion of the medical status of such workers Tabershaw<sup>5</sup> presented a comprehensive survey of 52 radium dial painters who worked a minimum of eighteen months in applying luminous paint. Their physical and dental conditions, their blood counts and their nutritional status were recorded, and the conclusion reached that reliance on medical examination is not sufficient to control the hazard. Only regular breath-radon analyses at intervals of six months or, in certain cases, of even three months, combined with an educational campaign regarding work habits, personal hygiene and care of teeth, can prevent deleterious effects.

Beta and gamma radiation is dealt with in a paper by Evans<sup>6</sup>. In textile and paper mills it is often necessary to install radioactive static eliminators as a safety appliance. These eliminators reduce the hazard of fire or explosion of chemical vapors by eliminating the possibility of electrical sparks due to static electricity. These safety appliances, however, being radioactive, present in themselves a new industrial hazard owing to the penetrating radiation that they may emit. Since the radiations that are generated and the maximum permissible doses are known, it is simply an engineering problem to provide adequate safety measures. Shields, sufficient distance and even magnetic deflection are recommended. The commercial de-

velopment of alpha-ray sources (plutonium, protactinium or polonium) that, unlike radium, emit few or no beta or gamma rays may in the future become a problem.

Injuries resulting from exposure to radioactive substances and roentgen rays are discussed by Dunlap<sup>7</sup>. The main hazards are encountered in plants where x-ray or radiologic equipment is manufactured or radioactive substances used. Safety measures consist in the elimination of all unnecessary exposures by the use of adequate lead shielding, long-handled instruments, speed in carrying out dangerous operations, the rotation of workers and, finally, careful medical supervision.

Out of Hanford also comes a most interesting paper by Cantril<sup>8</sup> on the use of radioactive tracers in industrial medicine. The method of employing a small quantity of a particular radioactive isotope to trace or tag the chemical flow or metabolic patterns in a chemical or physiologic process is not new and was used in various fields prior to the development of atomic energy. This procedure has been employed not only in physiology but also in industry. In the control of exposure of radium dial painters to radium it was possible to use the radioactive properties of the noxious agents in measuring the quantities of contamination on benches, floors, hands and so forth or in the air. The experienced industrial hygienist will with a little imagination recognize the possibilities of applying these technics to occupational hazards quite unrelated to the field of radioactive materials. A tracer could be found that, by virtue of its radiations, half-life and metabolic properties, would measure contamination of working locations and personnel. The method, however, will have to be controlled, not to substitute a radioactive toxin for a nonradioactive one.

The effects of electric injuries, with particular reference to the nervous system, are considered by Hyslop<sup>9</sup>. Accidental deaths from electricity (not due to lightning) represent 0.9 per cent of all accidental deaths, and about 0.4 per cent of all accidents in industry and in the home. Approximately 17 per cent or about 1 electric accident in 6 is fatal. Vital organs and tissues traversed by the current may be functionally impaired or even destroyed, and although other parts of the body may be affected with resulting functional or structural damage, persisting psychoneurotic reactions, as well as a permanent total disability, are rare. Electricity, in contrast to damage done by radium or radioactive substances, does not cause progressive dissemination or local degenerative structural defects.

#### THE SMALL PLANT

Industrial hygiene and industrial medicine are as necessary for the small plant as for the great industrial concerns. These small plants, however, which Bloomfield<sup>10</sup> calls "the underprivileged members of

the economic system," are often not able to provide an adequate medical department for health protection and health maintenance of their workers. It is essential that the achievements of modern industrial hygiene be made available to the small plant, for two thirds of American workers are employed in such plants. National and community health agencies in various states have therefore united with the small-plant employers and employees to bring about an improvement of worker health through control of his environmental hazards and his individual health problems. Millman et al.<sup>11</sup> report on the work of the Industrial Health Unit of New York City. Seven small plants, varying in size from 70 to 700 employees who had either inadequate or no health service, participated in the program. The results were satisfying. A program of this kind has proved to be economically feasible provided that proper plant organization can be installed and that official as well as unofficial community groups take an active interest in the success of the undertaking.

In California an industrial group — F. M. Poole, M. D., and Associates — has been formed to serve the industries in the growing industrial San Fernando Valley.<sup>12</sup> The staff of the group includes six physicians with extensive industrial experience, and the aim is to develop a comprehensive industrial medical plan designed specifically to benefit a variety of industries and plants of various size, down to the smallest, employing as few as ten workers.

How necessary it is to institute such health services for small plants and to enlist the interest of management, labor and community agencies in creating and maintaining it was proved by a survey conducted by the Bureau of Industrial Health of the State of New Jersey. Hazard<sup>13</sup> states that the results show that only 1 plant out of every 5 employing 101 persons or more and only half the plants employing 501 persons or more had adequate doctor service. Among plants employing 101 or more apiece 54 per cent did not offer physical examinations for either placement or health improvement, 65 per cent had no adequate plant food service, and nearly half — 43 per cent — were without a nurse.

Strong<sup>14</sup> insists that best results can be maintained if plant health service is based on the co-operation of management, labor, public-health agencies and special health agencies, which, in a common effort, can provide the protection and the medical care for the workers that the small plant is economically unable to afford. The installation and maintenance of a first aid kit under the control of one or more employees, especially trained in first aid techniques, is suggested for the small plant, store or shop where only 10 workers or less are employed. Although the careful maintenance of such a first-aid kit is unquestionably most important, however, it is un-

fortunately true that the indifference of both employer and employees probably makes such a kit often not only useless but a danger instead of a help.

In preventive medicine the small plant is also under a disadvantage compared to the large, industrial concerns. Pollak<sup>15</sup> compares conditions regarding tuberculosis in the Caterpillar Tractor Company of Peoria, Illinois, with those in smaller plants in the same area that do not maintain a full-time medical department. In the survey of 13,547 employees of the Caterpillar Tractor Company, the incidence of active pulmonary tuberculosis was 0.16 per cent. On the other hand, in the smaller plants covered by the same survey, of 12,129 employees given x-ray examinations, the case incidence of active pulmonary tuberculosis was 0.29 per cent, or nearly twice as high as that in the group that enjoyed the industrial health protection of a complete and comprehensive medical service.

The problem of the small plant in industrial medicine, being chiefly an economic one, must be solved by the co-operation of all concerned, including management, labor and the official and non-official health agencies.

### JOB PLACEMENT

During the war, virtually all able-bodied men having been taken into the armed forces, industry had to maintain vital production with a labor supply recruited from the ranks of the physically handicapped, the superannuated and women. It was found, however, that these physically inferior workers could and did achieve an excellent production record. The problem of the physically impaired worker has lost nothing of its urgency and significance in the postwar period.

Out of the war a new concept of industrial physical fitness has evolved. A worker is physically fit if he can do a good day's work. Harvey and Luongo<sup>16</sup> point out that the capacity for work is a relatively untouched problem and that medical science does not yet possess a method of evaluating it correctly. Ultimately, such capacity rests on the reserve compensation that the personality of the disabled worker provides. The examining industrial physician must therefore possess a certain diagnostic flair and must be able to judge the reserve compensation behind the visible fact of physical impairment. Although many doctors have evolved their personal formulas regarding the job placement of the handicapped, illuminating their rules with detailed charts, the insight of the examining physician will in the end prove of greater value than any purely schematic approach. In general, it is recommended that any doubt should be resolved in favor of the applicant, since the desire for the work oftener than not creates the capacity to perform the work. All studies on properly placed handicapped workers indicate that they are on a par with their able-

bodied fellow workers Training and placing costs are balanced by the fact that the handicapped workers stay on the job longer than the average able-bodied worker

Back strains, representing one of the most important problems in industrial medicine, have been investigated by Parton and Biram<sup>17</sup> These authors report on a series of a thousand consecutive routine roentgenograms of the lower back taken as part of a preplacement examination, 502 cases were considered normal, and anomalies were revealed in 498 The authors believe that these deformities play a significant role in the decompensation of backs in the age group over forty-five years, and in spite of the lack of knowledge regarding correlation with job placement, preplacement x-ray examination is useful These studies are in accord with similar studies by other investigators

Industry has to deal not only with disabled veterans and workers but also with physically unimpaired workers and their various problems Ghiselly<sup>18</sup> points out that the basic considerations in job placement and personnel procedures are not forms and schedules but rather men and women who have worked together in a complex social environment He also insists that job placement is not a static affair but a dynamic process that does not end with the assignment of a particular worker to a particular job New problems of adjustment, change in conditions and change in personality or attitude will constantly arise and make job placement a continuing process

Management has often found it advisable to employ a psychiatrist either in an in-plant or in a consultative capacity Clarke and Law<sup>19</sup> state that a few progressive concerns have always availed themselves of the services of a staff psychiatrist, but during the past few years, psychiatry in the field of industry has made great headway Psychiatric appraisal of the personality of the workers has been found of great value, not only in job-placement but also to combat absenteeism, undue work termination and accidents, which are often due more to faulty human material than to flaws in the technical department

Clarke and Law, as well as Leggo et al<sup>20</sup> reporting on their work in industrial psychiatry done at the Oak Ridge community where the atomic bomb was developed, speak of excellent results among thousands of employees It was found that psychologic and psychiatric pre-employment screening and the application of psychiatric insight in job assignments gave uniformly good results Therapy for on-the-job patients who presented emotional disturbances proved especially profitable, for it prevented non-disabling maladjustments from developing into major disabling breakdowns Leggo et al also state that during their two years' work at Oak Ridge they almost never encountered a patient with a major psychosis The bulk of the case load con-

sisted of anxiety states, reactive depressions and psychosomatic reactions It is safe to assume that similar conditions prevail in industry in general, and that with a minimum of treatment conspicuous on-the-job improvement can be achieved Such improvement, implying as it does adjustment not only to work conditions but also to home environment, makes the employment of the psychiatrist in the industrial field a gain for the entire community.

### DERMATITIS

Dermatitis continues to be the persistent problem of industrial hygiene, remaining in the forefront in the incidence of occupational diseases<sup>21</sup> It is occasionally encountered in unexpected places and from unexpected causes It has been universally accepted that dermatitis arising from irritant dusts, mists and vapors only develops if the irritating agent comes into actual contact with the skin Baker and White<sup>22</sup> report a case of occupational dermatitis due solely to the inhalation of trichloroethylene This solvent vapor, used as a degreasing material, was blown by several large fans directly into the open office of a foreman, who developed a severe dermatitis To establish that only inhalation and not penetration of the gas through clothing produced the dermatitis, the patient was sent to work wearing a gas mask When the mask was worn no skin irritation occurred, when the mask was discarded the dermatitis reappeared Installation of a ventilating system that dispersed the offending fumes through the roof cured the condition This is the first report of a case of generalized dermatitis produced solely by inhalation

It is generally accepted that scabies is transmitted only by direct contact. Fifteen women in a statistical department, however, contracted the disease through merely handling reports passed to them by a colleague suffering from the affliction, and the outbreak was deemed both occupational and compensable<sup>23</sup>

A number of authors discuss the causes of occupational dermatitis Klauder and Hardy<sup>24</sup> report on an additional 539 cases as a supplement to a previous report of 1113 cases of cutaneous diseases<sup>25</sup> The review of 2297 cases gives a comprehensive picture of the various causes of occupational dermatoses These causes are divided into seven groups according to the actual causative irritant and not according to occupation, as is the more usual procedure The authors believe that the listing by causes helps in suggesting preventive and investigative measures and facilitates teaching of the subject The irritants resulting most frequently in occupational dermatitis were solutions used in electroplating and compounds of chromium, the highest incidence rate occurred in the printing trades, electroplating, tanning, the manufacture of textiles and dyeing Primary irritants accounted for 24.8 per cent of cases, and sensitizers for 12.5 per cent

Other causes were trauma, wet work, solvents, oil and chlorinated hydrocarbons. Lane,<sup>26</sup> in a review of compensation paid for disability due to occupational dermatitis describes a steady increase in the incidence of dermatitis but a reduction in the lost time, average indemnity and cost of medical treatment of these cases. Peck<sup>27</sup> found the chief causes of industrial dermatitis to be petroleum products and greases, alkalies, cement and solvents, in the order listed.

Keil et al.<sup>28</sup> proved by patch test that the same ingredients that produce poison ivy are responsible for the dermatitis caused by cashew-nut-shell liquid. Both plants are members of the same plant family, Anacardiaceae, and persons sensitive to one plant are sensitive to the other. Cashew-nut-shell liquid is an agent that causes a great deal of difficulty, especially in stevedoring operations.

Schwartz and his associates<sup>29</sup> have developed an entirely new technic to determine the value of various commercial ointments supposed to withstand penetration by alkali, acid or oil. Three standard substances and twenty-seven commercial products were tested, and on the whole it was found that anhydrous wool fat and white petrolatum are quite as efficient protective measures as the best commercial products. This was true for protection against alkalies and acids, as well as for oil. Other authors observed certain commercial products to be effective. Excellent results have been reported from the use of Paraprol,<sup>30</sup> — a product consisting of urea, lauryl sulfoacetate and benzyl alcohol, — which was tested on 300 employees and found to be effective both as a prophylactic and as a therapeutic measure, no unfavorable reactions from its use have been observed.

Preventive measures from another angle are suggested by Klauder and Brill.<sup>31</sup> They attempted a correlation of the boiling ranges of some petroleum solvents with their dermatologic harmfulness. The irritant actions on the skin of petroleum fractions between kerosene and light spindle oil were dealt with, and the conclusion was reached that kerosene and solvents of lower boiling range invariably exert irritant action. The irritant action definitely decreased as the boiling range increased, and it therefore seems advisable to employ a product of as high a boiling range as possible consistent with the purpose for which it is to be used.

Protective clothing and personal hygiene are still of utmost importance to avoid undue exposure with resulting skin damage. Workers, as well as their foremen, must be educated to make conscientious use of the accepted preventive measures. Some of the methods used in the Army may be helpful in this educational endeavor. Personal or group talks, pamphlets, pictorial presentation and so forth can be utilized to explain and visualize the inevitable results of neglect and the equally indisputable rewards of proper care of the skin.

## SPECIFIC CHEMICALS

In dealing with the toxicity of the vast number of chemicals used in industry, the industrial physician is, above all, on the outlook for new and improved means to determine at an early stage the deleterious effects. The thymol barbitol test, which is reported by McCord and his co-workers,<sup>32</sup> is therefore of particular interest as a means of detecting toxic effects of carbon tetrachloride. Functional impairment has taken place on levels lower than 100 parts per 1,000,000, and it is even possible that in some cases death occurred from apparently trivial exposures. In 1944 MacLagan,<sup>33</sup> of England, found, in the course of an inquiry on the colloidal-gold reaction of serum, that thymol, introduced for antiseptic purposes into the barbitol employed as buffer along with certain serums, led to a turbidity apart from any action of the usual constituents of the colloidal-gold system. MacLagan<sup>34</sup> later established that this turbidity was quantitative and of diagnostic significance for hepatic dysfunction. McCord and his co-workers<sup>32</sup> showed that this test is of value in determining the action of carbon tetrachloride on the liver and other tissues. An investigation was made on 712 hospital patients and 82 normal persons. The results indicated that the quantitative association of increasing turbidity with hepatic injury appears well founded. Exposure to low levels of carbon tetrachloride vapors may cause functional changes and even organic injury. In animals, concentrations of 40, 60 and 80 parts of carbon tetrachloride per 1,000,000 produced thymol turbidity.

Although this work helps to determine minimal injury, the difficulty of measuring carbon tetrachloride vapors in the air has also been practically solved. Shayer and Ackerman<sup>35</sup> report a modified combustion method as used by the Army Industrial Hygiene Laboratory that permits the rapid and efficient determination of chlorinated hydrocarbon in air. Glass gas-sampling bulbs of capacities of 275 to 500 cc were used, and the collected vapors were burned in a modified sulfur lamp. The amount of hydrogen chloride formed was turbidimetrically determined with the help of a spectrophotometer. Four chlorinated hydrocarbons were studied, among them carbon tetrachloride, and it was found that concentration of vapor can be determined with an accuracy of 88 to 90 per cent.

Nutritional factors in industrial poisoning have been of interest for some time, especially regarding liver disease. Shaffer, Carpenter and Moses<sup>36</sup> report that, although methionine is of undoubted therapeutic and prophylactic value in the protection of protein-deficient animals against carbon tetrachloride poisoning, it exerts no protective action against the liver damage of normal animals poisoned with carbon tetrachloride.



Volatile hydrides that have toxicologic importance are dealt with by Webster<sup>37</sup> Whereas many of these compounds have no industrial application, it is quite likely that the rapidly increasing production of the rarer inorganic chemicals will lead to the use of a number of volatile hydrides Many of these compounds are of an insidious character, entering the body through inhalation, and it is necessary to recognize the potential danger from breathing the substances

An extensive study of the effects of beryllium compounds is offered by Hardy and Tabershaw<sup>38</sup> Seventeen cases of a puzzling disease, which the authors call "delayed chemical pneumonitis," appeared among the employees of a firm manufacturing fluorescent lamps In the course of the manufacture beryllium compounds were used, and although no clear etiology has been established, the weight of evidence indicates that beryllium was responsible The fact that the 17 workers affected were employed in one building during the same period clearly points to common exposure The clinical features of the disease are a delayed onset, intense dyspnea, marked loss of weight and unfavorable prognosis The relation of the acute form of this disease to the more chronic type has not yet been defined

The increased use of tellurium in industry has awakened a deeper interest in the problem of its effect on the organism De Meio<sup>39</sup> reports a series of animal experiments in which tellurium was fed to rats Although the low toxicity of elementary tellurium, as opposed to tellurate and tellurite, was again established, it seems that long exposure to tellurium in great concentration tends to lower normal increase in weight and growth

Ethylene dichloride is a chlorinated carbon that is widely used as a solvent and for other industrial purposes An extensive literature dealing with its toxicity, its peculiar ability to render the cornea turbid and the effects of various protective agents already exists Heppel et al<sup>40</sup> report the effects of daily inhalations of this gas on a variety of animals The results indicate that dichloroethane is one of the more toxic of the frequently used hydrocarbons and should be employed only when proper precautions are taken

Ketones, alcohols, esters, ethers and miscellaneous solvents, all used widely in industry, are the subject of a study by Silverman and his associates<sup>41</sup> in which sensory responses to these vapors were evaluated Sensory limits for eighteen organic solvents were established, and since eleven of these solvents had no previous evaluation of permissible concentration, the data offered are of special interest to the industrial hygienist and engineer

The report of a case of arsine poisoning by Hawlick and Ley<sup>42</sup> should be mentioned Freshly diluted hydrochloric acid, which had been treated with an inhibitor containing a soluble arsenic compound, was poured through a water jacket The operation

was carried out in a poorly ventilated room, and precautions against inhalations of fumes were not observed The employee exposed to the fumes experienced after a few hours severe hemoglobinuria, prostration, jaundice, an enlarged and tender liver, peripheral neuritis and distinct hemolytic anemia The tentative diagnosis of acute hemolytic anemia secondary to exposure to a heavy metal, possibly a compound of arsenic (arsine), was confirmed when a specimen of the metal pipe through which the acid had been poured was tested by the Army Industrial Hygiene Laboratory

An effective agent against industrial poisoning with arsenic and mercury has been discovered in BAL (British antilewisite) This compound, which was developed during the war as an antidote for lewisite, has proved successful in the treatment of arsenic poisoning of any type The drug (2-3 dimercaptopropanol) is the best from the standpoint of skin penetration when used as an ointment. Although the least dangerous of the thiols, it is quite toxic, and its use must be carefully controlled

#### MISCELLANEOUS CONDITIONS

Penicillin in two different forms has been found highly effective in group medicine in both the Army and the Navy Agmar<sup>43</sup> reports a study in which crude penicillin was inoculated into surgical-gauze dressings This preparation proved dramatically effective for such minor infections as boils, carbuncles, secondary epidermophytosis of the feet, eye and ear infections, chronic ulcers of the leg and infected cyst Crude penicillin solution and penicillin gauze did not cause any reactions and worked more rapidly than the sulfonamides These preparations are easy to make, readily transportable, simple to use and markedly potent

Levitt and Leathen<sup>44</sup> are equally enthusiastic about penicillin lozenges in the treatment of oral infections One hundred and seventeen patients with acute infection of the nasopharynx and tonsils were treated with penicillin lozenges of 500-unit strength each Results of the treatment were excellent Of the 117 patients, 110 were cured rapidly, 87 of them on an outpatient status Only 7 patients did not respond to the treatment Five of these cases had tonsillitis complicated by cervical adenitis, which evidently proved that local concentrations of penicillin cannot penetrate tonsillar crypts or reach infections deep in the tissue of lymph nodes

A program of malarial surveillance for the industrial physician is offered by Shillito<sup>45</sup> Industrial concerns expanding their interests and activities into tropical countries and war veterans returning from these regions make it necessary for a medical department to become familiar with effective methods of handling this problem Two possible courses are recommended either a careful surveillance without drug therapy or a course of daily doses of quinacrine



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## MASSACHUSETTS MEDICAL SOCIETY

### PROCEEDINGS OF THE ONE HUNDRED AND SIXTY-SIXTH ANNIVERSARY

May 20, 21, and 22, 1947

THE one hundred and sixty-sixth anniversary of the Massachusetts Medical Society was observed at the Hotel Statler in Boston on May 20, 21 and 22, 1947

Fifteen hundred and twenty-one physicians, one hundred ladies and two hundred and ninety-seven exhibitors were registered

The length of the meeting was increased this year by beginning the sessions in the morning of the first day instead of in the afternoon The Supervising Censors met in Parlor C at 4 30 p m on the afternoon of the previous day, May 19 This meeting was followed by the Cotting Supper in Parlors A and B, which was attended by 205 councilors The annual meeting of the Council was held in the Georgian Room at 7 00 p m with 189 councilors in attendance, as recorded in the attendance books

#### TUESDAY, MAY 20

The first general session, a symposium on industrial medicine, opened at 9 00 a m in the Georgian Room under the co-chairmanship of Dr. Daniel L. Lynch and Dr. Gerald L. Doherty

The one hundred and sixty-sixth annual meeting of the Society was held in the Georgian Room at 11 00 a m, President Dwight O'Hara presiding The attendance was about 450 Dr O'Hara spoke on "The State of the Society," after which the annual oration, "Medical Care in Our Free Society," was de-

livered by Dr Leland S McKittrick The annual luncheon was served in Parlors A, B and C to 101 fellows

The second general session, a symposium on medical care for the people of Massachusetts, was held in the Georgian Room at 2 00 p m under the co-chairmanship of Dr Reginald Fitz and Dr Albert A Hornor The Shattuck Lecture was delivered at 8 00 p m by Dr William Dock, of Brooklyn, New York, on the subject "Clinical Significance of Circulatory Peculiarities of Some of the Vital Organs" (This lecture appeared in the May 22, 1947, issue of the *Journal*)

#### WEDNESDAY, MAY 21

The third general session was held at 9-00 a m under the co-chairmanship of Dr Isaac S F Dodd and Dr Allen G Rice

At noon certain of the sections held their luncheons, followed by their annual meetings The Section of Medicine, under the chairmanship of Dr Francis C Hall, met in Parlor A The attendance was 110 The Section of Pediatrics, under the chairmanship of Dr Hyman Green, met in Parlor B, with 60 members in attendance at the luncheon and 84 at the scientific meeting following The Section of Dermatology and Syphilology met in Parlor C under the chairmanship of Dr Jacob H Swartz, with 43 in attendance at the luncheon and 55 at the

meeting The Section of Physiotherapy met in the Hancock Room under the chairmanship of Dr William D McFee, with 15 members present

At 2:00 p m the fourth general session, a symposium on bronchiectasis, was held in the Georgian Room under the co-chairmanship of Dr Richard H Sweet and Dr Louis H Nason

The annual dinner was held in the Georgian Room at 7:00 p m, with 418 in attendance The speaker of the evening was Dr Harrison H Shoulders, president of the American Medical Association, who delivered an address entitled "The Responsibilities of the Medical Profession"

#### THURSDAY, MAY 22

The fifth general session was held in the Georgian Room at 9:00 a m under the joint chairmanship of Dr Franklin G Balch, Jr, and Dr Walter E Garrey

At noon the remaining scientific sections held their luncheons and meetings The Section of Surgery under the chairmanship of Dr Alexander J A Campbell met in the Salle Moderne, with 100 in attendance The Section of Obstetrics and Gynecology under the chairmanship of Dr William J McDonald met in Parlor A, with 60 in attendance The Section of Radiology under the chairmanship of Dr Edward B D Neuhauser met in Parlor C, with 39 in attendance The Section of Anesthesiology under the chairmanship of Dr Sidney C Wiggins met in Parlor B, with 42 members attending

The sixth general session was held at 2:00 p m under the joint chairmanship of Dr Howard F Root and Dr Gordon M Morrison

There were eighty-nine technical and four scientific exhibits

On Wednesday, May 21, at 2:45 p m the Massachusetts Medico-Legal Society held its meeting concurrently in Parlor C

At the annual golf tournament held at the Woodland Golf Club on May 20, the low gross winner was Dr R J Nugent, the second gross winner, Dr M Sargent, the winner of the low net, Dr A D Crowell, and the winner of the second low net, Dr G Quigley An exhibition of works of art by members of the Massachusetts Physicians' Art Association was on view throughout the meeting

The special list of officers, standing and special committees, councilors, censors, admissions and deaths is appended

JOSEPH GARLAND, Secretary

#### ANNUAL MEETING OF THE SOCIETY

The one hundred and sixty-sixth annual meeting of the Massachusetts Medical Society was called to order by the president, Dr Dwight O'Hara, in the Georgian Room of the Hotel Statler, Boston, at 11:00 a m., May 20, 1947 Approximately 450 fellows were present.

The Secretary submitted the record of the last annual meeting held on May 22, 1946, as published in the September 19, 1946, issue of the *New England Journal of Medicine* It was moved and seconded that the record be accepted, and it was so ordered by vote of the fellows present

The Secretary reported that the membership of the Society as of May 22, 1946, was 5989, and as of May 20, 1947, it was 6256 During the year there had been a loss of 140 fellows—95 by death, 42 by resignation and 3 by deprivation of membership There had been a gain of 407, of which 403 were new members and 4 had been reinstated It was moved and seconded that the report be accepted, and it was so ordered by vote of the fellows

At the request of the President, the vice-president, Dr Isaac S F Dodd, assumed the chair, and Dr O'Hara gave the following address

One may come to the office of president-elect and later president of the Massachusetts Medical Society supposing himself to be somewhat familiar with its routine affairs But when one finds himself an *ex-officio* member of thirty-odd committees and begins to see the various ways in which their many interests cross, he can but stand and marvel at the volume and the continuity of the work accomplished year after year in the name of the Society It is an impressive, enlightening and pleasant experience After a preliminary intimation the mechanism of the Society begins to reveal itself there are a faithful few who toil at necessary basic tasks—our late lamented secretary, Dr Michael A Tighe our treasurer Dr Eliot Hubbard, our executive secretary Mr Robert St B Boyd our editor Dr Robert N Nye with his able assistants and their stenographic staff these turn the wheels, gears and cogs of the Massachusetts Medical Society

During the past year the machinery has needed some internal adjustments In October we lost by illness the services of Miss Katharine Cowles who had long kept our clerical house in order In January we took over by previous arrangement, our own office obligations and thus ended a period of years in which we had been dependent on the staff of the *New England Journal of Medicine* for whatever bookkeeping and stenography were needed In January we were first deprived of the services of our faithful secretary though happily we thought, he was able to direct us from afar while his coronary vessels rebuilt a collateral circulation But this was not to be He was able to make a few more visits to the headquarters of the Society, and attended several committee meetings during the early spring On April 8 the day before we expected him to join us again at 8 Fenway, Dr Tighe suddenly died.

We were warned but not prepared for this. Along with his sense of humor his kindly comradeship and his interest in every ramification of the Society, Dr Tighe has taken with him a knowledge of our affairs which surpassed that of any other man. These are the great losses of every organization—the contemporary intellects on which we depend, even thoughtlessly as we depend on roadways and bridges to get us about our daily work. We come to take them for granted and then they are gone. This was an irreparable loss. I ask the Society to stand for a moment of silent tribute to Secretary Michael A Tighe.

In the face of these adjustments the Society has been fortunate in its office personnel including among others Miss Margaret E Biggy Miss Elnor Kelley and especially Mr Boyd. How confidently a troubled institution may depend on the character and fidelity of a few individuals was vividly demonstrated to those of us who were close to these changes, and were naturally anxious to have the engines working smoothly while we were taking our turn at the steering wheel.

The one hundred and sixty-sixth year of the Massachusetts Medical Society is now closing An organization which has survived over such a period of time not only

has inevitable traditions and duties to which it must respond but also finds itself inevitably watched by other groups in the larger community of which it is a part. It must solve its problems not in its own interests alone but in the interests of the people as a whole. This is peculiarly true in our profession, and it is on this account that we tend to come to our decisions slowly. Much spade work must precede the actual conclusion of most of our business, and much spade work is now quietly going on, the result of which may not become apparent for months or years to come. In giving an account of business concluded by the Society, I therefore ask you to bear in mind that none of it is the fruit of a single year of effort, but is rather the natural conclusion of processes which have been initiated and prepared in preceding years. In like manner new business has been proposed and studied during the current year which can only be reported as in progress at the present moment.

#### *Veterans' Contract*

Late in 1945 the Veterans Administration evolved a new medical policy, under Generals Bradley and Hawley. The Administration's new policy had two main objectives — the staffing of its expanding hospital facilities, which was placed upon the shoulders of the Nation's medical schools, and the provision of home and office care for all veterans by doctors of their own choosing. Early in 1946 the Veterans Administration asked the Massachusetts Medical Society to undertake the responsibility for the latter function, and a committee under the chairmanship of Dr Humphrey L. McCarthy undertook what was to become a long and difficult task of orientation and negotiation. The Council devoted a special eight-hour meeting to the subject on April 10 and discussed it again on October 2, 1946. On October 26, agreements based on these discussions were reached with the Veterans Administration, and the matter was placed in the hands of the Blue Shield for administrative arrangements. The contract was signed and went into effect as of December 27, 1947, only to encounter the obstacle that the Blue Shield needed permissive legislation in order to carry out the contract. Opposition to such legislation has since appeared, and there have arisen other complications the details of which are not pertinent at this time. It should be emphasized here that the Massachusetts Medical Society is in no way compromised by these complications because it has sought and seeks nothing in the whole matter. The Society has merely responded and will continue to respond to every suggestion that it might be helpful to the interests of the veterans of this Commonwealth.

#### *Director of Medical Information and Education*

During 1945 several of the committees of the Society realized that it needed a more dynamic approach in its relations with the people, their legislators and their spokesmen, we were being socially misrepresented and misunderstood at a time when there was every reason for us to assert ourselves. A bill to license chiropractors reached Governor Tobin's desk, a nation-wide antivivisection effort vented itself in this state, among others, our motives in working for the establishment of the Medical Approving Authority were questioned, the call for postgraduate medical education was mounting beyond all available resources in the Commonwealth. These things led three of our committees to indicate their belief that the time had passed when the Society could depend on its committee members to meet without further aid the challenges of the day. President Fitz skillfully focused these needs for action with the result that the Council, on October 3, 1945, created a position to be known as Director of Medical Information and Education, and agreed to appoint such an officer on proposal by a special group, the Committee of Seven, named for the purpose by Dr Fitz. Finding an incumbent worthy of so great a task proved to be a difficult matter. The Committee of Seven worked for more than a year before they finally proposed to the Council, on February 5, that Dr John F. Conlin be named. Dr Conlin is to begin his duties on July 1, and we bespeak for him the interest and support of every fellow of the Society.

#### *Annual Assessment*

The employment of the Director of Medical Information and Education will throw the budget of the Society out of balance. The narrow margin by which we have been able to do business in recent years has been frequently commented on, and was brought before the Council with a proposal for increasing the annual assessment three years ago. At that time and since, certain unmet obligations of the Society have been discussed. A year ago the Council ordered the appointment of a special committee to study the entire problem and to report with recommendations. This report was placed before the Council on February 5, with recommendations of far-reaching importance to the future of the Society and the medical profession in the Commonwealth.

The committee recommended in principle that the Society employ a full-time secretary, that the Society support and thereby expand the usefulness of the Boston Medical Library, that financial support be arranged for needy widows and orphans of physicians, as well as for physicians themselves, that a retirement plan be established for full-time workers of the Society and that our present inadequate headquarters be expanded to provide at least sufficient committee rooms for the proper conduct of our business. The committee recommended an increase in the annual assessment from ten dollars to between twenty and twenty-five dollars. After approving the tentative program as outlined and carefully considering its implications in future expenditure, the Council voted on February 5 that the assessment be increased from ten to twenty-five dollars, beginning on January 1, 1948. In taking this action the Council extended our horizon beyond any to which we have been accustomed. The Society can now gaze out upon a field in which literary and sociologic responsibilities are accepted along with the scientific, educational and political interests of the past. If the world is to have a future it is apparent that the Massachusetts Medical Society intends to make itself a part of it.

#### *Postgraduate Education*

Over a period of years the Society has expressed an increasing interest in postgraduate medical education. This has been largely due to the excellent work of a committee under the chairmanship of Dr W. Richard Ohler. It has sometimes worked as a special committee and sometimes as a subcommittee under another name, such as medical defense, war participation or postwar planning. Whatever it has been called, it has done its job so well that each year our educational activities have been expanded, the high point having been reached in March and April of this year when more than 1200 doctors registered for forty-eight hours of instruction at Sanders Theater in Cambridge. Because this course alone was the equivalent of a complete college education for a score or more men we have been referring to Dr Ohler as "President of Sanders College" and to Dr Lewis M. Hurxthal as "Dean." Their curriculum included everything except football, and if it continues to increase in popularity they will be forced to adopt some athletic tactics in order to handle the crowds. In addition to these two there are of course scores of others who have willingly served, not only on the faculty of "Sanders College" but at the district meetings throughout the Commonwealth, at the meetings of the Postgraduate Assembly and on the programs now taking place here at the annual meeting. Altogether a formidable amount of postgraduate medical education is being provided for the doctors of Massachusetts by the fellows of the Society.

The Committee on Postgraduate Medical Education also has continued to operate the Bureau of Medical Information, which has been ably handled by Miss Mary D. Gaston at the Society Headquarters. This activity admirably met an early postwar need. What its future usefulness may be, however, is uncertain, we no longer have great numbers of medical strangers passing briefly through our midst, doctors are becoming established and tend to acquaint themselves individually with the local clinics and opportunities. The monthly cataloging of the greater Boston clinics is a helpful service, but to continue to operate the Bureau for this activity alone seems a little expensive.

*The State of the Society*

When I assumed the office of president a year ago, I received felicitations from a friend who pointed out that he had just completed fifty years of uninterrupted fellowship in the Massachusetts Medical Society. It occurred to me that such an event is significant in the life of any man or woman and is worthy of more than passing notice. Becoming interested I drew up a list of the fellows who were admitted to the Society in 1897, twenty two of these were still living. They had obviously passed the age at which they were entitled to retire by our by-laws, yet by consulting the records I found that eleven of them had retained continuous active fellowship over the period of fifty years. I have written to each of these eleven, hoping they could attend their fiftieth meeting. I now propose to read their names and if they are present I ask them to acknowledge that fact by rising.

Dr George A. Boucher of Brockton  
Dr John E. Fish, of Canton  
Dr Arthur P. George, of Haverhill  
Dr Joseph B. Howland of Hingham  
Dr Joseph I. Landay of Grafton  
Dr James F. Loughran, of Lowell  
Dr Franklin S. Newell of Boston  
Dr Ernest D. Pillsbury of Stoughton  
Dr Thomas B. Shaw, of Worcester  
Dr John B. Thomas, of Pittsfield  
Dr William J. Walton of Dorchester

We have no official award that we can make to these gentlemen, but I extend to them the hearty congratulations of the Society and I present their names to you as tangible evidence that the state of the Society is vigorous and sound.

Dr George A. Boucher, of Brockton, was present, and acknowledged the greeting of the Society.

The President resumed the chair, and as the next order of business introduced Dr Harrison H

Shoulders, president of the American Medical Association.

Dr O'Hara then introduced the delegates who were present from the other New England state medical societies—Dr Carl T. Phillips from Connecticut, Dr George E. Young from Maine and Dr Emery T. Porter from Rhode Island. Each acknowledged this introduction, and Dr Porter spoke as follows:

Dr O'Hara if your members have been reading the papers lately they have probably seen that Governor Bradford has recently called attention to the fact that there is an old Massachusetts law which states that any body coming from Rhode Island and Providence Plantations, the home of Roger Williams is subject to death on crossing the border into Massachusetts.

So I worried my way through the park this morning and did not get caught, and I welcome this chance to bring greetings from the State of Rhode Island where the Rhode Island Medical Society has just finished its one hundred and thirty sixth annual meeting.

The President next introduced the incoming officers, after which the one hundred and thirty-ninth annual oration, "Medical Care in Our Free Society," was delivered by Dr Leland S. McKittick. (The oration appeared in the June 19, 1947, issue of the *Journal*.)

Dr O'Hara declared the one hundred and sixty-sixth annual meeting of the Massachusetts Medical Society adjourned at 1:00 p.m.

JOSEPH GARLAND, *Secretary*

## APPENDIX

## OFFICERS FOR 1947-1948

President Edward P. Bagge, Holyoke, 207 Elm St.  
President Elect Daniel B. Reardon, Quincy, 1186 Hancock St.  
Vice-President Charles J. Kickham, Brookline Office, Boston, 508 Commonwealth Ave.  
Secretary Joseph Garland, Brookline Office, Boston (15) 8 Fenway  
Treasurer Eliot Hubbard Jr., Cambridge, 29 Highland St.  
Assistant Treasurer Norman A. Welch, West Roxbury Office, Boston, 520 Commonwealth Ave.  
Orator Allen S. Johnson, Springfield, 276 Bridge St.

## COMMITTEES ELECTED BY THE DISTRICTS

Executive Committee of the Council—Established 1941 (members ex-officio and one counselor and alternate elected by the councilors of each district medical society)  
President—Edward P. Bagge, Holyoke, 207 Elm St.  
President Elect—Daniel B. Reardon, Quincy, 1186 Hancock St.  
Vice-President—Charles J. Kickham, Brookline Office, Boston, 508 Commonwealth Ave.  
Secretary—Joseph Garland, Brookline Office, Boston (15) 8 Fenway  
Treasurer—Eliot Hubbard Jr., Cambridge, 29 Highland St.

## Term Expires 1948

Essex South—Walter G. Phippen, Salem, 31 Chestnut St. (Alternate: Bernard Appel, Lynn, 281 Ocean St.)  
Hampshire—Henry A. Tadgell, Belchertown, Belchertown State School (Alternate: Lawrence N. Durbin, Amherst, 66 Amity St.)  
Middlesex South—Harold G. Giddings, Newton Centre Office, Boston (16) 270 Commonwealth Ave. (Alternate: Arthur M. Jackson, Everett, 49) 512 Broadway)

Norfolk South—Fred A. Bartlett, Wollaston (70) 308 Beale St. (Alternate: Harry Braverman, Quincy (69) 43 School St.)  
Suffolk—Alexander J. A. Campbell, Boston (15) 520 Commonwealth Ave. (Alternate: Howard F. Root, Boston (15) 81 Bay State Rd.)  
Worcester—Bancroft C. Wheeler, Worcester, 27 Elm St. (Alternate: Franklin P. Bousquet, Worcester, 390 Main St.)

## Term Expires 1949

Barnstable—Paul M. Butterfield, Harwich. (Alternate: Paul P. Henson, Hyannis, 149 Main St.)  
Bristol North—Joseph L. Murphy, Taunton, 23 Cedar St. (Alternate: Curtis B. Kingsbury, Taunton, 63 Prospect St.)  
Bristol South—Richard B. Butler, Fall River, 278 North Main St. (Alternate: Curtis C. Tripp, New Bedford, 416 County St.)  
Essex North—Roll C. Norris, Methuen, 247 Broadway. (Alternate: George J. Connor, Haverhill, 81 Merrimack St.)  
Middlesex East—Kenneth L. MacLachlan, Melrose, 1 Belle Vue Ave. (Alternate: Justin L. Anderson, Reading, 53 Woburn St.)  
Plymouth—George A. Moore, Brockton, 167 Newbury St. (Alternate: John C. Angley, Bryantville, School St.)

## Term Expires 1950

Berkshire—John Hughes, Pittsfield, 74 North St. (Alternate: Edward Wyman, Great Barrington, 244 Main St.)  
Franklin—Lawrence R. Dame, Greenfield, 78 Federal St. (Alternate: Frank W. Dean, East Northfield, 185 Main St.)  
Hampden—Archibald J. Douglas, Westfield, 50 Court St. (Alternate: Frederic Hagler, Springfield, 20 Maple St.)  
Middlesex North—William M. Collins, Lowell, 174 Central St. (Alternate: Artemas J. Stewart, Lowell, 310 Merrimack St.)

**NORFOLK** Charles J E Kickham, Jamaica Plain Office, Brookline, 1101 Beacon St. (Alternate Carl Bearse, Boston, 483 Beacon St.)

**WORCESTER NORTH** John J Curley, Leominster, 89 West St. (Alternate George P Keaveny, Fitchburg, 62 Fox St.)

**Committee on Nominations** — Established 1874 (one councilor and alternate elected yearly by each district medical society)

**BARNSTABLE** Paul M Butterfield, Harwich (Alternate Paul P Henson, Hyannis, 149 Main St.)

**BERKSHIRE** John Hughes, Pittsfield, 74 North St. (Alternate N Newall Copeland, Pittsfield, 131 North St.)

**BRISTOL NORTH** Joseph L Murphy, Taunton, 23 Cedar St. (Alternate Curtis B Kingsbury, Taunton, 63 Prospect St.)

**BRISTOL SOUTH** Henry Wardle, Fall River, 173 Purchase St. (Alternate Donald R Mills, Edgartown, Box 654)

**ESSEX NORTH** Charles F Warren, Amesbury, 155 Main St. (Alternate Percy J Look, Andover, 115 Main St.)

**ESSEX SOUTH** Peer P Johnson, Beverly, 1 Monument Square (Alternate O S Pettingill, Middleton, Essex Sanatorium)

**FRANKLIN** John E Moran, Greenfield, 15 Franklin St. (Alternate Warren D Thomas, Montague, Central St.)

**HAMPDEN** George L Schadt, Springfield, 44 Chestnut St. (Alternate George L Steele, Springfield, 20 Maple St.)

**HAMPSHIRE** Henry A Tadgell, Belchertown, Belchertown State School (Alternate Lawrence N Durgin, Amherst, 66 Amity St.)

**MIDDLESEX EAST** Edward M Halligan, Reading, 37 Salem St. (Alternate John M Wilcox, Woburn, 6 Bennett St.)

**MIDDLESEX NORTH** William F Ryan, Lowell, 219 Central St. (Alternate William M Collins, Lowell, 174 Central St.)

**MIDDLESEX SOUTH** Harold G Giddings, Newton Centre Office, Boston, 270 Commonwealth Avenue (Alternate Fred R Jouett, Cambridge, 1 Craigie St.)

**NORFOLK** Albert Ehrenfried, Brookline Office, Boston (15), 520 Commonwealth Ave (Alternate Carlton E Allard, Dorchester, 428 Columbia Rd)

**NORFOLK SOUTH** Henry A Robinson, Hingham, 205 North St. (Alternate Frederick Hinchliffe, Cohasset, 117 South Main St.)

**PLYMOUTH** Bradford H Peirce, South Hanson, Plymouth County Hospital (Alternate Alfred L Duncombe, Brockton, 38 Winthrop St.)

**SUFFOLK** Albert A. Hornor, Boston (15), 319 Longwood Ave. (Alternate Conrad Wesselhoeft, Boston, 315 Marlboro St.)

**WORCESTER** Ralph S Perkins, Worcester, 10 Hackfeld Rd (Alternate Franklyn P Bousquet, Worcester, 390 Main St.)

**WORCESTER NORTH** John J Curley, Leominster, 89 West St. (Alternate James V McHugh, Leominster, 55 West St.)

**Committee on Public Relations** — Established 1939 (one councilor elected yearly by each district medical society, the president and president-elect of the Society are chairman and vice-chairman, respectively, and the vice-president and secretary of the Society are members ex-officio)

**BARNSTABLE** Paul P Henson, Hyannis, 149 Main St.

**BERKSHIRE** Patrick J Sullivan, Dalton, 417 Main St.

**BRISTOL NORTH** Milton E Johnson, Attleboro, 33 Bank St.

**BRISTOL SOUTH** Harold E Perry, New Bedford, 159 Cottage St.

**ESSEX NORTH** Harold R Kurth, Lawrence, 57 Jackson St.

**ESSEX SOUTH** Bernard Appel, Lynn, 281 Ocean St.

**FRANKLIN** Howard M Kemp, Greenfield, 42 Franklin St.

**HAMPDEN** Frederic Hagler, Springfield, 20 Maple St.

**HAMPSHIRE** Joseph R. Hobbs, Williamsburg, Main St.

**MIDDLESEX EAST** Milton J Quinn, Winchester, 44 Church St.

**MIDDLESEX NORTH** Samuel A Dibbins, Lowell, 528 Andover St.

**MIDDLESEX SOUTH** Ralph H Wells, Lexington, 1430 Massachusetts Ave

**NORFOLK** Dean S Luce, Canton, 553 Washington St.

**NORFOLK SOUTH** Henry A Robinson, Hingham, 205 North St.

**PLYMOUTH** Charles D McCann, Brockton, 12 Cottage St.

**SUFFOLK** Howard F Root, Boston, 81 Bay State Rd

**WORCESTER** Nicholas S Scarcello, Worcester, 1 Sheldon St.

**WORCESTER NORTH** James V McHugh, Leominster, 55 West St.

## Subcommittees of Committee on Public Relations

### TAX-SUPPORTED MEDICAL CARE — Established 1940

Thomas Hunter (Worcester), *chairman*, Frederick S Hopkins, Hampden, Albert A Hornor, Suffolk, William J Pelletier, Franklin, and Frank W Snow, Essex North

### COMMITTEE TO MEET WITH THE MEDICAL ADVISORY COMMITTEE OF THE INDUSTRIAL ACCIDENT BOARD — Established 1942

Gordon M Morrison (Middlesex South), *chairman*, Charles H Bradford, Suffolk, Joseph H Burnett, Middlesex South, Somers Fraser, Suffolk, and William W Teahan, Hampden

### POSTPAYMENT MEDICAL CARE — Established 1942

Norman A Welch (Norfolk), *chairman*, Fred A. Bartlett, Norfolk South, Michael F Barrett, Plymouth, James H Brewster, Bristol North, James T Brogan, Worcester, Lucien R Chaput, Essex North, Charles F Fasce, Berkshire, Patrick E. Gear, Hampden, Loring Grimes, Essex South, Francis T. Jantzen, Suffolk, Egon E Kattwinkel, Middlesex South, Howard M Kemp, Franklin, William B LeBrecht, Worcester North, Wilfred L McKenzie, Middlesex East, Harold E. Perry, Bristol South, Henry A Robinson, Norfolk South, Harold F Rowley, Barnstable, and Elmer E Thomas, Hampshire.

### Committee on Legislation — Established 1942 (one councilor elected yearly by each district medical society)

**BARNSTABLE** Julius G Kelley, Pocasset, Barnstable County Sanatorium

**BERKSHIRE** John Hughes, Pittsfield, 74 North St.

**BRISTOL NORTH** William M Stobbs, Attleboro, 63 Bank St.

**BRISTOL SOUTH** Curtis C Tripp, New Bedford, 416 County St.

**ESSEX NORTH** Nicandro F DeCesare, Methuen. Office, Lawrence, 57 Jackson St

**ESSEX SOUTH** Loring Grimes, Swampscott, 84 Humphrey St.

**FRANKLIN** Harold R Mahar, Orange, 1 High St.

**HAMPDEN** Arthur H Riordan, Indian Orchard, 147 Oak St.

**HAMPSHIRE** Lawrence N Durgin, Amherst, 66 Amity St.

**MIDDLESEX EAST** John M Wilcox, Woburn, 6 Bennett St.

**MIDDLESEX NORTH** A Warren Stearns, Billerica

**MIDDLESEX SOUTH** Kenneth J Tillotson, Belmont. Office, Waverley, McLean Hospital

**NORFOLK** Solomon L Skvirsky, Chestnut Hill Office, 546A

State House, Boston

**NORFOLK SOUTH** David L Belding, Hingham, 215 Main St.

**PLYMOUTH** Alfred L. Duncombe, Brockton, 38 Winthrop St.

**SUFFOLK** William E Browne, Boston (15), 587 Beacon St.

**WORCESTER** George R. Dunlop, Worcester, 53 Massachusetts Ave (chairman)

**WORCESTER NORTH** John J Curley, Leominster, 89 West St.

## Subcommittee of the Committee on Legislation

### NATIONAL LEGISLATION — Established 1946

Elmer S Bagnall (Essex North), *chairman*, David L Belding, Norfolk South, Vlado A Getting, Middlesex South, Donald Munro, Suffolk, and Augustus Thorndike, Suffolk

## STANDING COMMITTEES FOR 1946-1947

### ELECTED BY THE COUNCIL, MAY 19, 1947

*Date of Appointment*

### Publications — Established 1825

Richard M Smith, Suffolk June 6, 1933 (appointed chairman May 21, 1941)  
May 21, 1941

Oliver Cope, Middlesex South  
John Fallon, Worcester November 14, 1944

James P O'Hare, Suffolk June 9, 1936

Conrad Wesselhoeft, Suffolk June 2, 1937

### Arrangements — Established 1849

G Guy Bailey, Jr, Middlesex South November 13, 1942 (appointed chairman May 19, 1947)  
Franklin G Balch, Jr, Suffolk May 19, 1947

Gordon A. Donaldson May 19, 1947  
 Middlesex South  
 Harold G. Giddings, May 22, 1944  
 Middlesex South  
 John W. Norcross, May 19, 1947  
 Middlesex South

#### Ethics and Discipline — Established 1871

Ralph R. Stratton, June 9, 1936 (appointed  
 Middlesex East chairman May 21, 1941)  
 William J. Brickley, Suffolk February 3, 1937  
 Archibald R. Gardner, May 21, 1941  
 Middlesex North  
 Fred R. Jouett, May 21, 1940  
 Middlesex South  
 Allen G. Rice, Hampden June 1, 1938

#### Medical Education — Established 1881

Chester S. Keefe, Suffolk February 4, 1942 (appointed  
 chairman May 19, 1947)  
 James M. Faulkner, Norfolk May 21, 1946  
 George D. Henderson, June 1, 1938  
 Hampden  
 Isaac R. Jankelson, Norfolk May 25, 1942

#### Membership — Established 1897

Peirce H. Leavitt, Plymouth June 1, 1938 (appointed  
 chairman September 3, 1946)  
 May 23, 1945  
 William A. R. Chapin, Hampden  
 Lewis S. Pilcher, Middlesex South July 26, 1946  
 Guy L. Richardson, Essex North May 21, 1946  
 Samuel N. Vose, Suffolk March 15, 1944  
 (Albert E. Parkhurst, Essex South, James M. Baty, Middle-  
 sex South; C. Bertram Gay, Worcester North, — repre-  
 senting the Supervising Censors)

#### Public Health — Established 1912

Roy J. Ward, Worcester May 22, 1944 (chairman)  
 John J. Poutas, May 21, 1946  
 Middlesex South  
 Warren R. Sisson, Suffolk May 19, 1947  
 Lawrence J. Smith, Hampden May 19, 1947  
 Conrad Wesselhoeft, Suffolk July 27, 1944

#### Subcommittee of the Committee on Public Health

MENTAL HEALTH — Established 1947  
 Walter E. Barton, Norfolk February 5, 1947 (chairman)  
 William Melamed, February 5, 1947  
 Worcester  
 Henry A. Tadgell, February 5, 1947  
 Hampshire

#### Medical Defense — Established 1927

Horatio Rogers, Suffolk June 7, 1939 (appointed  
 chairman May 19, 1947)  
 June 7, 1927  
 Edwin D. Gardner, Bristol South  
 Charles J. Kickham, May 21, 1946  
 Norfolk  
 John E. Moran, Franklin May 19, 1947  
 William R. Morrison, June 9, 1936  
 Suffolk

#### Finance — Established 1938.

Robert W. Buck, May 21, 1946 (chairman)  
 Middlesex South  
 Francis C. Hall, Suffolk July 8, 1943  
 Fabian Packard, May 21, 1946  
 Middlesex South  
 Bancroft C. Wheeler, May 21, 1946  
 Worcester  
 Charles F. Wilinsky, June 2, 1938  
 Suffolk

#### Society Headquarters — Established 1942.

Frank R. Ober, Suffolk May 22, 1944 (appointed  
 chairman November 1, 1944)  
 November 6, 1944  
 Albert A. Hornor, Suffolk May 21, 1946  
 Walter G. Phippen,  
 Essex South

Daniel B. Reardon May 22, 1944  
 Norfolk South  
 George L. Steele, Hampden May 19, 1947

#### Industrial Health — Established 1942.

Daniel L. Lynch, Norfolk May 25, 1942 (appointed  
 chairman May 21, 1946)  
 Joseph C. Aub, Suffolk May 25, 1942  
 Louis R. Daniels, May 22, 1944  
 Middlesex South  
 John G. Downing, May 22, 1944  
 Middlesex South  
 Harold R. Kurth, Essex North May 23, 1945  
 Frederic N. Manley, May 19, 1947  
 Norfolk South  
 Henry C. Marble, Suffolk May 19, 1947

#### Advisory Committee to Committee on Industrial Health — Established 1942.

Philip Drinker  
 Harriet L. Hardy  
 Emma S. Tountant

#### SPECIAL COMMITTEES FOR 1947-1948

ELECTED BY THE COUNCIL, May 19, 1947

#### Cancer — Established 1917

Shields Warren Suffolk, *chairman* Thomas J. Anglem,  
 Suffolk Ernest M. Daland Suffolk, Allen G. Rice  
 Hampden and Channing C. Simmons, Suffolk.

#### To Consider Expert Testimony — Established 1936

Francis P. McCarthy Norfolk, *chairman*, Carl Bearse,  
 Norfolk William J. Brickley, Suffolk Frank R.  
 Ober, Suffolk and William H. Robey, Suffolk.

#### To Meet with the Massachusetts Hospital Association — Established 1940.

Albert E. Parkhurst Essex South, *chairman* Edward A.  
 Adams, Worcester North, Edwin D. Gardner,  
 Bristol South Frederic Hagler Hampden Justin E.  
 Hayes, Hampshire and Nicholas S. Scarcello,  
 Worcester

#### Maternal Welfare — Established 1941

Duncan Reid Middlesex South, *chairman*, James M.  
 Baty Middlesex South Arthur F. G. Edgelow,  
 Hampden Samuel B. Kirkwood Middlesex East  
 Florence L. McKay Suffolk Louis E. Phaneuf  
 Suffolk and Raymond S. Titus Norfolk.

#### Rehabilitation — Established 1941

Joseph H. Shortell Suffolk, *chairman* Benjamin F.  
 Andrews, Worcester, Ralph M. Chambers, Bristol  
 North William M. Collins Middlesex North  
 James J. Regan Suffolk and Arthur L. Watkins  
 Middlesex South

#### Council Rules — Established 1944

Charles E. Mongan Middlesex South *chairman* Elmer  
 S. Bagnall Essex North, Frank R. Ober Suffolk,  
 George L. Schadt, Hampden, and Albert A. Hornor  
 Suffolk.

#### Postgraduate Medical Education — Established 1944

W. Richard Ohler Norfolk, *chairman* George A.  
 Buckley, Plymouth Vlado A. Getting Middlesex  
 South, Robert H. Goodwin, Bristol South Lewis M.  
 Hursthal, Suffolk George P. Keaveny Worcester  
 North Leo F. King, Middlesex North (interim  
 appointment) Charles G. Mixer Suffolk Robert  
 N. Nye, Suffolk, Joseph W. O'Connor Worcester  
 Samuel H. Proger, Norfolk George S. Reynolds,  
 Berkshire, James L. Smead Hampden, Harry C.  
 Solomon, Suffolk, and Henry D. Stebbins, Essex  
 South.

#### Medical Economics — Established 1944

Leland S. McKinnick, Suffolk, *chairman*; Elmer S.  
 Bagnall, Essex North Allan M. Butler Suffolk  
 Vlado A. Getting Middlesex South and Merrill C.  
 Soaman Suffolk.



**Postwar Loan Fund — Established 1945**

George L. Schadt, Hampden, *chairman*, Eliot Hubbard, Jr., Middlesex South, Charles C. Lund, Suffolk, Stephen A. Mahoney, Hampden, and Albert E. Parkhurst, Essex South

**Physical Medicine — Established 1945**

Arthur L. Watkins, Middlesex South, *chairman*, Alexander P. Aitken, Middlesex East, Ralph M. Chambers, Bristol North, Franklin P. Lowry, Middlesex South, and Henry A. Taddell, Hampshire

**To Make Recommendations as to Future Directors of Blue Shield — Established 1945**

Leland S. McKittrick, Suffolk, *chairman* (term expires 1949), Harold G. Giddings, Middlesex South (term expires 1951), Elliott P. Joslin, Suffolk (term expires 1952), Peirce H. Leavitt, Plymouth (term expires 1950), and George G. Smith, Suffolk (term expires 1948)

**To Meet with General Hawley with View of Formulating Program in Massachusetts for Medical Care of Veterans and Dependents — Established 1945**

Humphrey L. McCarthy, Norfolk, *chairman*, James K. Bragger, Norfolk, and Allen S. Johnson, Hampden

**To Confer with the Massachusetts Farm Bureau Federation — Established 1945**

Joseph C. Merriam, Middlesex South, *chairman*, John E. Moran, Franklin, and Elmer E. Thomas, Hampshire

**To Make a Survey of Malpractice Insurance in Massachusetts — Established 1946**

Carl Bearse, Norfolk, *chairman*, William J. Brickley, Suffolk, Edwin D. Gardner, Bristol South, Daniel B. Reardon, Norfolk South, and Guy L. Richardson, Essex North

**To Assist the Council on Medical Education and Hospitals of the American Medical Association in the Provisional Approval of Certain Massachusetts Hospitals — Established 1946**

Robert T. Monroe, Norfolk, *chairman*, Laurence D. Chapin, Hampden, H. Quimby Gallupe, Middlesex South, Walter G. Phippen, Essex South, and Charles F. Wilinsky, Suffolk

**Veterans' Affairs — Established 1946**

G. Philip Grabfield, Suffolk, *chairman*, Victor G. Balboni, Suffolk, George P. Denny, Suffolk, Alexander Marble, Suffolk, and George F. Wilkins, Middlesex South

In addition the following are representatives from the various district medical societies

Charles H. Bradford, Suffolk

Stephen Brown, Hampshire

William M. Carr, Plymouth

Leo R. Desmond, Norfolk

Spencer C. Flo, Franklin

Merrill F. Gardner, Bristol South

Willis M. Gowen, Middlesex East

Leonard W. Hill, Bristol North

Sheldon L. Hunt, Barnstable

Thomas Hunter, Worcester

Edwin M. Mahoney, Hampden

John C. McGirr, Middlesex South

Frank P. Morse, Jr., Essex South

Franklin K. Paddock, Berkshire

Ensio K. F. Ronka, Norfolk South

Louis B. Simard, Essex North

Thomas J. G. Tighe, Middlesex North

Charles A. Wheeler, Worcester North

**Postgraduate Assembly — Established 1946**

Leroy E. Parkins, Suffolk, *chairman*, Harold G. Giddings, Middlesex South, Frederick S. Hopkins, Hampden, Charles J. Kickham, Norfolk, and Robert N. Nye, Suffolk

**To Study Income Level for Blue Shield — Established 1946**

Charles F. Wilinsky, Suffolk, *chairman*, Norman H. Bruce, Middlesex South, Raoul L. Drapeau, Middlesex North, Henry L. Kirkendall, Worcester, and John W. Spellman, Norfolk

**To Establish a Pension Plan — Established 1947**

Robert W. Buck, Middlesex South, *chairman*, Eliot Hubbard, Jr., Middlesex South, Robert N. Nye, Suffolk, and George W. Papen, Norfolk

**Advisory Committee on School Medical Services — Established 1947**

Stewart Clifford, Middlesex South, Elmer S. Bagnall, Essex North, Joseph Garland, Suffolk, Florence McKay, Suffolk, Ernest Morris, Middlesex South, Thomas F. Reilly, Hampden, and James O. Wail, Worcester

**To Study Special Services — Established 1947**

Blue Cross Elmer S. Bagnall, Mr. Reginald F. Cahalan, Blue Shield Arthur W. Allen, Charles G. Hayden, Massachusetts Hospital Association Mr. Frank Wing, Rev. Donald A. McGowan, Dr. Charles F. Wilinsky, Massachusetts Medical Society Leland S. McKittrick, *chairman*, Joseph Garland, *secretary*, Radiologists Merrill C. Sosman, Hugh F. Hare, Pathologists G. Kenneth Mallory, Donald A. Nickerson, Anesthesiologists Urban H. Eversole, Sidney C. Wiggins

**Auditing**

Howard B. Jackson, Norfolk, *chairman*, and Frank T. Downey, Middlesex South

**Representatives to the Massachusetts Central Health Council**

Elmer S. Bagnall, Essex North, *chairman*, James W. Bunce, Berkshire, Merrill E. Champion, Suffolk, Earle M. Chapman, Suffolk

**Representative to the Hospital Council of Boston for the Year 1947**

William E. Browne, Suffolk

**Representative on the Legislative Committee of the Massachusetts Central Health Council**

John F. Conlin, Suffolk

**Representative on a Professional Advisory Committee Organized by the Division of Vocational Rehabilitation of the State Department of Education for the Purpose of Establishing a Program of Physical Restoration**

Joseph H. Shortell, Suffolk

**Representatives to the Council of the New England State Medical Societies**

Archibald J. Douglas, Hampden, Gerald N. Hoeftel, Middlesex South, and Norman A. Welch, Norfolk

**Representative for Survey by Academy of Pediatrics**

Gerald N. Hoeftel, Middlesex South

**Twenty-Five Voting Members in Massachusetts Hospital Service, Inc.**

Benjamin H. Alton, Worcester, Gerardo M. Balboni, Suffolk, Laurence D. Chapin, Hampden, Lucien R. Chaput, Essex North, George K. Fenn, Essex South, Joseph E. Flynn, Middlesex South, Archibald R. Gardner, Middlesex North, Harold G. Giddings, Middlesex South, Henry W. Godfrey, Middlesex South, Albert A. Hornor, Suffolk, John H. Lambert, Middlesex North, Alexander A. Levi, Middlesex South, Raymond A. McCarthy, Middlesex South, Joseph C. Merriam, Middlesex South, Donald Munro, Suffolk, Albert E. Parkhurst, Essex South, Lewis S. Pitcher, Middlesex South, Helen S. Pittman, Suffolk, Allen G. Rice, Hampden, Arthur T. Ronan, Norfolk, George L. Steele, Hampden, Ralph R. Stratton, Middlesex East, John E. Talbot, Worcester, and Edward L. Young, Norfolk

# DELEGATES AND ALTERNATES TO THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION FOR 1947-1948

## Delegates

## Alternates

June 1 1946 to June 1, 1948

David D. Scannell, Norfolk	Elmer S. Bagnall Essex North
Dwight O'Hara Middlesex South	William J. Pelletier Franklin
Charles E. Alonagan Middlesex South	Patrick E. Gear Hamden
Walter G. Phippen, Essex South	John I. B. Vail Barnstable

June 1 1947 to June 1, 1949

Charles J. Kichham, Norfolk	John Fallon Worcester
Leland S. McKinnick Suffolk	Patrick J. Sullivan Berkshire

## COUNCILORS FOR 1947-1948

(ELECTED BY THE DISTRICT MEDICAL SOCIETIES AT THEIR ANNUAL MEETINGS APRIL 15 TO MAY 15 1946)

## Barnstable

H. P. Hopkins, Chatham, V. P.  
P. M. Butterfield, Harwich, E. C. M. N. C.  
P. P. Henson Hyannis, 149 Main St., A. E. C.  
A. M. N. C., P. R. C.  
J. G. Kelley Pocasset, Barnstable County Sanatorium  
Leg. C.  
Frederick Sanborn Osterville Bates Ave., Sec.  
John I. B. Vail, Hyannis 155 Main St.

## Berkshire

Modesto Criscitello Pittsfield 28 North St. V. P.  
D. N. Beers Pittsfield 74 North St. Sec.  
N. N. Copeland Pittsfield 131 North St. A. M. N. C.  
J. F. Flynn, Pittsfield 28 North St.  
John Hughes Pittsfield 74 North St., E. C. M. N. C.,  
Leg. C.  
C. T. Leslie, Pittsfield, 18 Bank Row  
N. B. McWilliams Williamstown, 56 Spring St.  
Helen M. Scoville, Pittsfield House of Mercy Hospital  
P. J. Sullivan, Dalton 471 Main St. P. R. C.  
E. R. Wyman Great Barrington 259 Main St. A. E. C.

## Bristol North

J. V. Chaugny Taunton, 43 West Britannia St. V. P.  
W. E. Dawson Taunton 58 Winthrop St. Sec.  
M. E. Johnson Attleboro 33 Bank St. P. R. C.  
C. B. Kingsbury Taunton, 63 Prospect St. A. E. C.  
A. M. N. C.  
J. L. Murphy Taunton 23 Cedar St., E. C. M. N. C.  
W. M. Stobbs Attleboro 63 Bank St. Leg. C.

## Bristol South

G. W. Blood Fall River 82 New Boston Rd., V. P.  
R. B. Butler, Fall River, 278 No. Main St. E. C.  
J. C. Corrigan Fall River, 422 No. Main St.  
J. E. Fell Fall River 181 Purchase St. Sec.  
J. A. Fournier Fall River 11 Choate St.  
E. D. Gardner, Marion, Box 175  
R. H. Goodwin, New Bedford 15 South 6th St.  
William Mason Fall River, 151 Rock St.  
D. R. Mills Edgartown Pease Point Way A. M. N. C.  
H. E. Perry, New Bedford 159 Cottage St., P. R. C.  
C. C. Tripp New Bedford, 416 County St. A. E. C.  
Leg. C.  
Henry Wardle, Fall River, 173 Purchase St. M. N. C.

## Essex North

L. C. Pearce, Newburyport, 279 High St., V. P.  
H. M. Allen, Lawrence, 301 Essex St.  
E. S. Bagnall, Groveland 281 Main St. Ex Pres. C.  
R. V. Bakel, Methuen, 7 Hampshire St.  
G. J. Connor Haverhill, 81 Merrimack St., A. E. C.  
Elizabeth Councilman Newburyport, 83 High St.  
N. F. DeCesare, Lawrence, 57 Jackson St. Leg. C.  
H. A. Fenton Lawrence, 36 Winthrop Ave.  
A. P. George, Haverhill 78 Chestnut St.  
H. R. Kuth, Lawrence, 57 Jackson St. Sec., P. R. C.  
P. J. Look, Andover 115 Main St. A. M. N. C.

R. C. Norris, Methuen 247 Broadway E. C.  
G. L. Richardson, Haverhill 94 Emerson St.  
F. W. Snow, Newburyport, 24 Essex St.  
C. F. Warren, Amesbury 1 School St. M. N. C.

## Essex South

L. F. Box, Beverly 39 Broadway, V. P.  
Bernard Appel, Lynn 281 Ocean St., P. R. C., A. E. C. -  
W. W. Babson, Gloucester 79 Prospect St.  
K. J. Chadwell Swampscott, 26 Lexington Circle  
R. E. Foss Peabody 125 Main St.  
S. E. Goulding Beverly 38 Ocean St.  
Loring Grimes, Swampscott, 84 Humphrey St. Leg. C.  
C. A. Herneck Manchester 21 Union St.  
W. R. Irving Gloucester 35 Middle St.  
P. P. Johnson, Beverly, 1 Monument Square, M. N. C.  
B. B. Mansfield, Ipswich, 4 Green St.  
A. E. Parkhurst, Beverly 1 Monument Square C.  
O. S. Pettingill, Middleton Essex Sanatorium A. M. N. C.  
W. G. Phippen, Salem 31 Chestnut St., Ex Pres. E. C.  
E. D. Reynolds, Danvers, 48 High St.  
J. R. Shaughnessy Salem, 24½ Winter St.  
H. D. Stebbins, Salem 342 Essex St. Sec.  
P. E. Tivnan, Salem 70 Washington St.  
C. F. Twomey, East Lynn, 80 Ocean St.  
C. A. Worthen, Lynn, 19 Park St.

## Franklin

J. B. Temple, Shelburne Falls 11 Main St. V. P.  
H. L. Craft, Ashfield, Sec.  
L. R. Dame, Greenfield 78 Federal St. E. C.  
F. W. Dean East Northfield 185 Main St. A. E. C.  
H. M. Kemp, Greenfield 42 Franklin St. P. R. C.  
H. R. Mahar, Orange, 1 High St. Leg. C.  
J. E. Moran, Greenfield 31 Federal St. M. N. C.  
W. D. Thomas, Montague, Central St. A. M. N. C.

## Hamden

A. F. G. Edgelow Springfield 76 Maple St. V. P.  
F. H. Allen Holyoke, 16 Fairfield St.  
E. P. Bagg, Holyoke, 207 Elm Street, President.  
R. L. Barrett, Springfield 21 Maple St.  
H. F. Byrnes Springfield - 6 Chestnut St.  
W. A. R. Chapin Springfield, 121 Chestnut St.  
J. L. Cherekin Springfield, 333 Bridge St.  
A. J. Douglas Westfield 30 Court St. E. C.  
E. C. Dubois, Springfield, 174 Buckingham St.  
P. E. Gear Holyoke, 188 Chestnut St.  
Frederic Hagler Springfield 20 Maple St. A. E. C.  
P. R. C.  
G. D. Henderson Holyoke, 176 Chestnut St.  
F. S. Hopkins Springfield 146 Chestnut St.  
Charles Jurat, Springfield 70 Chestnut St.  
R. T. Miller, Ware 89 Main St.  
John Pallo Westfield 97 Elm St.  
A. G. Rice Springfield, 146 Chestnut St.  
A. H. Riordan, Indian Orchard 147 Oak St. Leg. C.  
G. L. Schadt Springfield 44 Chestnut St. Ex Pres.  
M. N. C., C.  
J. A. Seaman Longmeadow Office Springfield 20  
Maple St.  
G. C. Steele West Springfield 39 Upper Church St. Sec.  
G. L. Steele, Springfield 20 Maple St. A. M. N. C.  
W. W. Teahan, Holyoke, 217 Essex St.

## Hampshire

J. J. Curran Northampton, 16 Centre St., V. P.  
L. N. Durgin Amherst, 66 Amity St., A. E. C.,  
A. M. N. C. Leg. C.  
J. R. Hobbs Williamsburg Main St., P. R. C.  
L. B. Pond Easthampton 115 Main St.  
F. Mary P. Snook, Worthington Sec.  
H. A. Taggell, Belchertown Belchertown State School  
E. C., M. N. C.

## Middlesex East

D. L. Joyce Woburn 269 Main St. V. P.  
J. L. Anderson, Reading 53 Woburn St., A. E. C.  
T. P. Devlin Stoughton 38 Pleasant St.  
Robert Dutton, Wakefield 33 Avon St.  
E. M. Halligan, Reading 37 Salem St. M. N. C.  
R. W. Layton Melrose 8 Porter St., Sec.  
K. L. Macdachlan Melrose 76, 1 Bellevue Ave. E. C.  
M. J. Quinn, Winchester 44 Church St. P. R. C.  
R. R. Stratton Melrose, 538 Lynn Fells Parkway  
J. M. Wilcox, Woburn 6 Bennett St., Leg. C., A. M. N. C.

**Middlesex North**

C S Baker, Lowell, 8 Merrimack St., V P  
 R E Cole, Westford  
 W M Collins, Lowell, 174 Central St., E C, A M N C  
 S A Dibbins, Lowell, 528 Andover St., P R C  
 L J Hall, Lowell, 8 Merrimack St.  
 B D Leahey, Lowell, 9 Central St., Sec  
 W F Ryan, Lowell, 219 Central St., M N C  
 A W Stearns, Billerica, Leg C  
 A J Stewart, Lowell, 310 Merrimack St., A E C

**Middlesex South**

J F Casey, Allston Office, Boston 15, 475 Commonwealth Ave., V P  
 G G Bailey, Jr., Boston, 412 Beacon St., C  
 E W Barron, Malden 48 Office, Boston, 20 Ash St  
 Harris Bass, Everett 49, 351 Broadway  
 J M Baty, Belmont. Office, Brookline 46, 1101 Beacon St.  
 J D Bennett, West Somerville 44, 72 College Ave  
 W O Blanchard, Newton 58, 465 Centre St  
 H K Bloom, Everett, 17 Kenwood Rd  
 G F H Bowers, Newton Highlands 61, 156 Woodward St.  
 Alice M Broadhurst, Watertown, 259 Mt. Auburn St.  
 Madelaine R Brown, Cambridge. Office, Boston 16, 264 Beacon St.  
 R N Brown, Malden, 621 Main St.  
 R W Buck, Waban Office, Boston 15, 5 Bay State Rd., C  
 E J Butler, Cambridge, 25 Garden St.  
 C W Clark, Newtonville 60, 363 Walnut St  
 E A Cooney, Newton Office, Boston 16, 270 Commonwealth Ave  
 W H Crosby, Brighton, 304 Faneuil St.  
 J A Daley, Natick, 36 Pond St.  
 C L Derick, Newton Highlands Office, Boston 15, 412 Beacon St.  
 J G Downing, Newton Office, Boston 15, 520 Commonwealth Ave.  
 A G Engelbach, Cambridge, 330 Mt. Auburn St.  
 W C Feeley, Cambridge, 859 Massachusetts Ave  
 C W Finnerty, West Somerville 44, 440 Broadway  
 H Q Gallupe, Waltham 54, 751 Main St.  
 F W Gay, Malden, 20 Park St.  
 V A Getting, Belmont. Office, Boston, 546 State House  
 H G Giddings, Newton Centre Office, Boston 16, 270 Commonwealth Ave., E C, M N C  
 H W Godfrey, Auburndale 66, 14 Hancock St.  
 J L Golden, Medford 55, 86 Forest St  
 A D Guthrie, Medford 55, 408 Salem St  
 Eliot Hubbard, Jr., Cambridge, 29 Highland St., Treasurer  
 A M Jackson, Everett, 512 Broadway, A E C  
 F R Jouett, Cambridge, 1 Craigie St., A M N C  
 Sylvester B Kelley, West Newton, 34 Exeter St  
 A A Levi, Newton Office, Boston 15, 481 Beacon St., Sec.  
 A N Makechnie, Cambridge, 14 Upland Rd  
 R A. McCarty, Waltham 54, 465 Lexington St.  
 J H McSweeney, Somerville, 26 Bow St.  
 J C Merriam, Framingham, 198 Union Ave., C  
 Dudley Merrill, Cambridge, 51 Brattle St.  
 C. E Mongan, Somerville, 24 Central St., Ex-Pres, C  
 G M Morrison, Waban Office, Boston 15, 520 Commonwealth Ave., C  
 J P Nelligan, Cambridge, 2336 Massachusetts Ave.  
 E J O'Brien, Jr., Newton Office, Boston 16, 270 Commonwealth Ave  
 Dwight O'Hara, Waltham Office, Boston 15, 416 Huntington Ave., Ex-Pres  
 Fabyan Packard, Belmont, 154 Washington St.  
 L G Paul, Newton Centre. Office, Boston 16, 270 Commonwealth Ave.  
 L S Pilcher, Newton Centre 59, 43 Parker St.  
 Randolph Piper, Concord, 14 Sudbury Rd  
 T E Reilly, Marlboro, 6 Newton St.  
 Max Ritvo, Newton Office, Boston 15, 416 Marlboro St.  
 G A. Saunders, Arlington, 50 Pleasant St.  
 M J Schlesinger, Newton Office, Boston 15, 330 Brookline Ave.  
 E. W Small, Belmont, 68 Leonard St.

H P Stevens, Cambridge, 1 Craigie St.  
 K J Tillotson, Waverley, McLean Hospital, Leg C.  
 A B Toppan, Watertown, 289 Mt. Auburn St.  
 J H Townsend, Belmont, 195 Marsh St.  
 J E Vance, Natick Office, Boston 15, 29 Bay State Rd.  
 C F Walcott, Cambridge, 81 Sparks St.  
 A L Watkins, Arlington Office, Boston 14, Massachusetts General Hospital, C  
 R H Wells, Lexington, 1430 Massachusetts Ave., P R C  
 B M Wein, Newton Office, Boston 15, 471 Commonwealth Ave.  
 B S Wood, Weston Office, Waltham 54, 751 Main St.  
 Alfred Worcester, Waltham 54, 314 Bacon St., Ex-Pres.  
 Hovhannes Zovickian, Watertown, 528 Mt. Auburn St.

**Norfolk**

Carl Bearse, Boston 15, 483 Beacon St., V P, A. E. C., C  
 A. A. Abrams, Brookline 46, 153 Dean Rd  
 C E Allard, Dorchester, 428 Columbia Rd, A M N C  
 G R. Allen, Norwood, 449 Washington St.  
 B E Barton, West Roxbury 32, 10 Richwood St., Sec.  
 Elizabeth Broyles, Wellesley, Simpson Infirmary  
 J H Cauley, Dorchester, 8 Carruth St.  
 L R Desmond, Milton, 1272 Brook Rd  
 G L Doherty, West Roxbury Office, Boston 15, 466 Commonwealth Ave.  
 Albert Ehrenfried, Brookline. Office, Boston 15, 520 Beacon St., M N C  
 J M Faulkner, Brookline. Office, 80 East Concord St., Boston  
 Susannah Friedman, Roxbury Office, Boston 15, 485 Commonwealth Ave.  
 T R. Goethals, Brookline, 34 Hawthorn Rd  
 D L Halbersleben, Brookline 46, 42 Goodnough Rd  
 J B Hall, Roxbury 19, 108 Dudley St.  
 H. B Harris, East Milton Office, Dorchester, 487 Columbia Rd  
 R J Heffernan, Jamaica Plain Office, Brookline, 1101 Beacon St.  
 Gilbert Horrax, Brookline Office, Boston, 605 Commonwealth Ave.  
 P J Jakmauh, Milton Office, South Boston 27, 509 Broadway  
 I R Jankelson, Jamaica Plain Office, Boston 15, 483 Beacon St.  
 C J Kickham, Brookline. Office, Boston 15, 508 Commonwealth Ave., Vice-Pres  
 C. J E Kickham, Jamaica Plain Office, Brookline, 1101 Beacon St., E. C  
 D L Lionberger, Dedham, 709 East St.  
 D S Luce, Canton, 553 Washington St., P R C  
 C M Lydon, Dorchester, 276 Bowdoin St.  
 D L Lynch, Roslindale. Office, Boston, 245 State St., C  
 T F P Lyons, Milton Office, Boston 16, 270 Commonwealth Ave.  
 F P McCarthy, Milton. Office, Boston 15, 371 Commonwealth Ave.  
 H L McCarthy, West Roxbury Office, Boston 15, 479 Beacon St., C.  
 R. T Monroe, Brookline Office, Boston 16, 270 Commonwealth Ave., C.  
 F J Moran, Dedham, 395 Washington St  
 H R Morrison, Wellesley Office, Boston, 370 Marlboro St.  
 Hyman Morrison, Brookline. Office, Boston 15, 483 Beacon St.  
 D J Mullane, Brookline 46, 1101 Beacon St.  
 H A. Novack, Brookline. Office, Boston, 471 Commonwealth Ave  
 J J O'Connell, Dorchester, 1061 Dorchester Ave  
 W R Ohler, Jamaica Plain Office, Boston 15, 319 Longwood Ave., C  
 E E O'Neil, Brookline. Office, Boston, 270 Commonwealth Ave.  
 G W Papan, Brookline Office, Boston, 31 Milk St.  
 H C Petterson, West Roxbury Office, Boston 15, 29 Bay State Rd  
 S H Proger, Brookline. Office, Boston, 30 Bennet St.  
 Frederick Reis, Jamaica Plain Office, Boston 15, 416 Huntington Ave.  
 H A Rice, Canton, 742 Washington St.

S. A. Robins, Boston 15, 636 Beacon St.  
D. D. Scannell, Jamaica Plain. Office, Boston 15 475 Commonwealth Ave.  
J. A. Seth, Milton. Office, Boston 15 47 Bay State Rd.  
J. A. Sieracki, Norwood 71 Winter St.  
S. L. Skirsky, Chestnut Hill. Office, Boston, 336 State House, Leg. C.  
E. C. Smith, Brookline. Office Boston 1 20 Commonwealth Ave.  
Kathleyn S. Snow, Jamaica Plain. Office Boston 15, 466 Commonwealth Ave.  
J. W. Spellman, Chestnut Hill. Office, Brookline, 1101 Beacon St.  
A. R. Stagg, Medfield 25 Pleasant St.  
W. J. Walton, Dorchester 106 Bowdoin St.  
N. A. Welch, West Roxbury. Office, Boston 1 520 Commonwealth Ave. Asst. Treas., C.  
P. R. Withington, Milton 330 Randolph Ave.  
Marjorie Woodman, Jamaica Plain. Office Boston, 21 Bay State Rd.  
E. T. Wyman, Brookline. Office Boston 15 319 Longwood Ave.

## Norfolk South

R. L. Cook, Quincy 1245 Hancock St. V P  
A. E. Bartlett, Wollaston 70 308 Beale St., E. C.  
D. L. Belding, Hingham 215 Main St., Leg. C.  
Harry Braverman, Quincy 69 43 School St., A. E. C.  
E. M. Britton, Wollaston, 25 Elm Ave.  
W. R. Helfrich Quincy 69, 166 Washington St.  
Frederick Hinchcliffe, Cohasset 117 South Main St., A. M. N. C.  
E. K. Jenkins, South Braintree, Norfolk County Hospital Sec.  
N. R. Pillsbury, South Braintree, Norfolk County Hospital.  
D. B. Reardon, Quincy 69, 1186 Hancock St., President-Elect.  
H. A. Robinson, Hingham 205 North St. P. R. C., M. N. C.  
R. G. Vinal, Norwell, Main St.

## Plymouth

R. C. McLeod, Brockton, Goddard Hospital, V P  
J. C. Angley, Bryantville, School St. A. E. C.  
A. L. Duncombe, Brockton 38 Winthrop St., A. M. N. C., Leg. C.  
Samuel Gale, Brockton, The Checkerton Sec.  
W. C. Gould, Kingston, 214 Main St.  
P. H. Leavitt, Brockton, 129 West Elm St., C.  
C. D. McCann, Brockton 12 Cottage St., P. R. C.  
G. A. Moore, Brockton 167 Newbury St., E. C.  
B. H. Peirce, South Hanson Plymouth County Hospital M. N. C.  
E. L. Perry, Middleboro 39 Oak St.

## Suffolk

C. C. Lund, Boston 15 20 Gloucester St. V P  
H. L. Albright, Boston 15 412 Beacon St.  
T. J. Anglem, Brookline, 1180 Beacon St.  
C. H. Bradford, Boston, 220 Beacon St.  
W. J. Brickley, Boston 15 524 Commonwealth Ave.  
W. E. Browne, Boston 15, 587 Beacon St. Leg. C.  
A. M. Butler, Boston 14, Massachusetts General Hospital.  
A. J. A. Campbell, Boston 15, 520 Commonwealth Ave., E. C.  
E. M. Chapman, Brookline. Office Boston, 266 Beacon St.  
Henry Clifford, Cambridge, 21 Lowell St.  
A. P. DerHagopian, Chelsea 39 Cary Ave.  
H. H. Faxon, Brookline. Office Boston 264 Beacon St.  
N. W. Faxon, Boston 14 Massachusetts General Hospital.  
Jacob Fine, Boston 15, 330 Brookline Ave.  
Maurice Fremont-Smith, Boston 15 12 Hereford St.  
Joseph Garland, Boston 16 266 Beacon St., Secretary  
G. Lynde Garely, East Boston, 624 Bennington St.  
A. A. Horner, Boston 15 319 Longwood Ave. M. N. C.

C. S. Keefe, Boston 65 East Newton St. C.  
H. A. Kelly, Winthrop 200 Pleasant St.  
T. H. Lamm, Boston 15 700 Longwood Ave.  
\*C. F. Marshall, Boston 276 Commonwealth Ave.  
F. W. Marlow, Jr., Brookline 1284 Beacon St.  
Donald Munroe, Boston 15 818 Harrison Ave.  
H. L. Musgrave, Revere, 620 Beach St.  
R. N. Ave, Boston 1 2 Fenway  
F. R. Over, Boston, 24 Marlboro St., C.  
F. W. O'Brien, Boston 1 475 Beacon St.  
J. P. O'Hare, Boston 15 5.0 Commonwealth Ave.  
L. E. Parkins, Boston 1 12 Bay State Rd., C.  
L. E. Phaneuf, Boston 16 270 Commonwealth Ave.  
Helen S. Pittman, Boston 16, 264 Beacon St.  
J. H. Pratt, Boston 11 50 Benet St.  
J. J. Regan, South Boston. Office Boston, 520 Commonwealth Ave.  
Horatio Roberts, Boston 264 Beacon St., C.  
H. F. Root, Boston 15 81 Bay State Rd., A. E. C., P. R. C.  
Wyman Richards, Jr., Newton Centre. Office, Boston, 264 Beacon St.  
C. G. Shedd, Boston 422 Beacon St., Sec.  
R. M. Smith, Boston 33 Dartmouth St., C.  
C. M. Stearns, Chelsea 116 Hawthorn St.  
Augustus Thorndike, Boston 15 319 Longwood Ave.  
Conrad Wesselschoff, Boston, 715 Marlboro St., A. M. N. C.

## Worcester

F. R. Carr, Worcester 27 Elm St., V P  
A. W. Atwood, Worcester 390 Main St.  
George Ballantyne, Worcester, 27 Elm St.  
F. P. Bouquet, Worcester, 390 Main St., A. E. C., A. M. N. C.  
J. J. Cohen, Worcester 340 Main St.  
E. J. Crane, Holden, Armington Lane.  
Paul Dufault, Rutland, Rutland State Sanatorium  
G. R. Dunlop, Worcester 53 Massachusetts Ave., Leg. C.  
W. J. Elliott, Worcester, 119 Belmont St.  
John Fallon, Worcester 390 Main St.  
L. M. Felton, Worcester, 36 Pleasant St.  
R. H. Goodale, Worcester, 46 Otisgo Rd.  
Thomas Hunter, Shrewsbury, 545 Main St., C.  
H. L. Kirkendall, Worcester, 27 Elm St.  
J. A. Lundy, Oxford 26 Main St.  
D. A. McClusky, Worcester 7 Hawthorne St.  
J. M. Olson, Westboro, 54 West Main St.  
F. A. O'Toole, Clinton 181 Chestnut St.  
R. S. Perkins, Worcester, 27 Elm St. M. N. C.  
E. L. Richmond, Worcester 390 Main St.  
N. S. Scarcello, Worcester 1 Sheldon St. P. R. C.  
R. F. Sullivan, Worcester 54 Hillcroft Ave.  
J. J. Tegelberg, Worcester 390 Main St., Sec.  
G. C. Tully, Worcester 1 Cedar St.  
R. J. Ward, Worcester 9 Bellevue St., C.  
B. C. Wheeler, Worcester, 27 Elm St., E. C.

## Worcester North

J. C. Hales, Gardner, 183 Lawrence St. V P  
J. J. Curley, Leominster 89 West St., E. C. M. N. C., Leg. C.  
C. B. Gale, Fitchburg, 62 Day St.  
G. P. Heavens, Fitchburg 62 Fox St. A. E. C.  
C. N. McPeak, Fitchburg 18 Hartwell St.  
J. V. McHugh, Leominster, 55 West St., A. M. N. C., P. R. C.  
J. G. Simmons, Fitchburg 30 Myrtle Ave., Sec.

The initials E. C. following the name of a Councillor indicate that he is a member of the Executive Committee and of E. C. that he is an alternate member of the Executive Committee. A. M. N. C. that he is a member of the Committee on Nominations and J. M. N. C. that he is an alternate member of the Committee on Nominations; Leg. C. that he is a member of the Committee on Legislation; P. R. C. that he is a member of the Committee on Public Relations; P. that a member is a councillor by virtue of his office as president of a district society and so vice-president of the general society; C. by virtue of his office as chairman of a standing committee; Sec. by virtue of his office as secretary of a district society and Ex-Officio by virtue of being a past president.

\*Interim appointment

## CENSORS FOR 1947-1948

**Barnstable**

P P Henson, Hyannis, *supervisor*  
 D H Hiebert, Provincetown  
 D E Higgins, Barnstable  
 Joseph Kelley, Orleans  
 O S Simpson, Barnstable

**Berkshire**

C T Leslie, Pittsfield, *supervisor*  
 I S F Dodd, Pittsfield  
 A C England, Pittsfield  
 W T Frawley, Pittsfield  
 A M Gangemi, North Adams

**Bristol North**

J L Murphy, Taunton, *supervisor*  
 J H Brewster, Attleboro  
 C B Kingsbury, Taunton  
 A J Leddy, Taunton  
 H G Vaughan, Attleboro

**Bristol South**

Henry Wardle, Fall River, *supervisor*  
 F M Howes, New Bedford  
 W F MacKnight, Fall River  
 E A McCarthy, Fall River  
 C C Persons, New Bedford

**Essex North**

R V Baketel, Methuen, *supervisor*  
 M F Ames, Newburyport  
 F C Atkinson, North Andover  
 L C Peirce, Newburyport  
 L B Simard, Haverhill

**Essex South**

A E Parkhurst, Beverly, *supervisor*  
 H N Baker, Rockport  
 S N Gardner, Salem  
 W C Inman, Danvers  
 C F Twomey, Lynn

**Franklin**

J E Moran, Greenfield, *supervisor*  
 J P Collieran, South Deerfield  
 F W Dean, Northfield  
 H R Mahar, Orange  
 W J Pelletier, Turners Falls

**Hampden**

A A. Palermo, Springfield, *supervisor*  
 J M Gilchrist, Springfield  
 G D Henderson, Holyoke  
 John Pallo, Westfield  
 J L Smead, Springfield

**Hampshire**

L B Pond, Easthampton, *supervisor*  
 Stephen Brown, Northampton  
 M E Cooney, Northampton  
 T F Corriden, Northampton  
 J E Hayes, Northampton

**Middlesex East**

S H Moses, Winchester, *supervisor*  
 C R Baisley, Reading  
 H A Bouve, Wakefield  
 T P Devlin, Stoughton  
 J H Fay, Melrose

**Middlesex North**

W F Ryan, Lowell, *supervisor*  
 L F King, Lowell  
 E H Iatham, Lowell  
 H L Leland, Lowell  
 J D Sweeney, Lowell

**Middlesex South**

J M Baty, Belmont, *supervisor*  
 Oliver Cope, Cambridge  
 H J Crumb, Lexington  
 E A Gaston, Framingham  
 J F Williams, Everett

**Norfolk**

Kathlevne S Snow, Jamaica Plain, *supervisor*  
 C E Allard, Dorchester  
 I R Jankelson, Jamaica Plain  
 H A Novack, Brookline  
 E E O'Neil, Chestnut Hill

**Norfolk South**

F A Bartlett, Wollaston, *supervisor*  
 Arthur Rapoport, Quincy  
 H S Reid, Cohasset  
 R E Ross, South Braintree  
 W L Sargent, Quincy

**Plymouth**

E L Perry, Middleboro, *supervisor*  
 L A Alley, Lakeville  
 Jacob Brenner, North Easton  
 F B Gilmore, Brockton  
 R E Swenson, Plymouth

**Suffolk**

J H Pratt, Boston, *supervisor*  
 John F Collins, Revere  
 R L Goodale, Boston  
 L M Hurxthal, Boston  
 J J Todd, Boston

**Worcester**

B C Wheeler, Worcester, *supervisor*  
 J B Butts, Worcester  
 E J Crane, Holden  
 H L Kirkendall, Worcester  
 J W McKoan, Jr., Worcester

**Worcester North**

C B Gav, Fitchburg, *supervisor*  
 K J Jolma, Gardner  
 J W Mason, Ashburnham  
 S I Nathanson, Fitchburg  
 A B Skelton, Winchendon

## VICE-PRESIDENTS OF THE MASSACHUSETTS MEDICAL SOCIETY (*Ex-Officio*) FOR 1947-1948

### PRESIDENTS OF DISTRICT MEDICAL SOCIETIES

(Arranged according to seniority of fellowship in the Massachusetts Medical Society)

**Bristol South** — George W Blood, Fall River  
**Middlesex North** — C Stoyke Baker, Lowell  
**Middlesex South** — John F Casey, Boston  
**Norfolk** — Carl Bearse, Boston  
**Suffolk** — Charles C Lund, Boston  
**Hampden** — Arthur F G Edgelow, Springfield  
**Middlesex East** — Daniel L Joyce, Woburn  
**Bristol North** — Joseph V Chatigny, Taunton  
**Berkshire** — Modestino Criscitiello, Pittsfield  
**Worcester North** — Jesse C Hales, Gardner  
**Plymouth** — Ralph C McLeod, Plymouth  
**Norfolk South** — Robert L Cook, Quincy  
**Essex North** — Lincoln C Peirce, Newburyport  
**Essex South** — Leonard F Box, Beverly  
**Worcester** — Frank B Carr, Worcester  
**Franklin** — John B Temple, Shelburne Falls  
**Hampshire** — John J Curran, Northampton  
**Barnstable** — Henry P Hopkins, Chatham

## COMMISSIONERS OF TRIAL FOR 1947-1948

Barnstable — F O Cass Provincetown  
 Berkshire — J B Thomas Pittsfield  
 Bristol North — J W Cook, Mansfield  
 Bristol South — A. C. Lewis, Fall River  
 Essex North — F W Anthony Haverhill  
 Essex South — O C Blair Lynn  
 Franklin — R W D Jacobus Turners Falls  
 Hampden — F K Dutton Springfield  
 Hampshire — R C Byrne Hatfield  
 Middlesex East — I W Richardson Wakefield  
 Middlesex North — C M Roughan Lowell  
 Middlesex South — H P Stevens Cambridge  
 Norfolk — W J Walton Dorchester  
 Norfolk South — W L Sargent Quincy  
 Plymouth — J A Carriulo Brockton  
 Suffolk — D G Anderson Boston  
 Worcester — W P Bowers Clinton  
 Worcester North — W E. Curner Leominster

## OFFICERS OF THE SECTIONS FOR 1947-1948

## Medicine

Chairman Francis C Hall Boston vice-chairman  
 Laurence B. Ellis, Boston secretary Allen S. John-  
 son, Springfield.

## Surgery

Chairman, George S. Reynolds Pittsfield secretary  
 Robert E. Gross, Boston  
 Executive Committee — John W. Spellman Brookline  
 Charles C. Lund, Boston Langdon Parsons Newton

## Pediatrics

President, Lewis W. Hill Boston secretary Gerald N.  
 Hoeft, Boston and Cambridge.  
 Executive Committee — Leroy T. Stokes Haverhill  
 Floyd R. Smith Pittsfield Hyman Green Boston.

## Obstetrics and Gynecology

Chairman, Arthur T. Hertig Boston, vice-chairman  
 James F. Conway Brookline secretary Daniel J.  
 McSweeney Milton.

## Radiology

Chairman Hugh F. Hare, Newton and Boston secretary  
 Albert M. Moloney, West Roxbury and Boston

## Physiotherapy

Chairman, William D. McFee Haverhill secretary  
 Henry A. Taddell Belchertown

## Dermatology and Syphilology

Chairman Austin W. Cheever Boston secretary Maurice  
 M. Tolman, Chelsea.

## Anesthesiology

Chairman, Urban H. Eversole Boston secretary Morris  
 J. Nicholson, Boston.

OFFICERS OF THE DISTRICT MEDICAL SOCIETIES FOR  
1947-1948

Barnstable — President Henry P. Hopkins, Chatham  
 vice-president Arthur J. D. Ellis, Harwich Port secretary Fred-  
 erick Sanborn Barnstable treasurer Frank Traversa, Barn-  
 stable, librarian Carroll H. Keane Chatham executive coun-  
 cilor and public relations councilor Paul P. Henson, Hyannis.  
 Berkshire — President, Modestino Crisantiello, Pittsfield  
 vice-president, George S. Reynolds, Pittsfield secretary  
 Daniel N. Biers, Pittsfield treasurer Theodore W. Jones  
 Pittsfield legislative councilor, John Hughes Pittsfield  
 public relations councilor Patrick J. Sullivan, Dalton.

Bristol North — President Joseph V. Chaugny Taunton  
 vice president, James H. Brewster Attleboro secretary  
 William E. Dawson, Taunton, treasurer Charles E. Hoyer,  
 Taunton executive councilor J. L. Murphy Taunton, legisla-  
 tive councilor William M. Stobbs, Attleboro, public relations  
 councilor M. E. Johnson Attleboro

Bristol South — President, George W. Blood, Fall River  
 vice president Aubrey J. Pothier, New Bedford secretary  
 and treasurer James E. Fell Fall River executive councilor  
 Richard B. Butler Fall River, legislative councilor Curtis C.  
 Tripp New Bedford public relations councilor, Harold E.  
 Perry New Bedford

Essex North — President Lincoln C. Pearce, Newbury  
 port vice president, Robert E. Blais, Amesbury secretary  
 Harold R. Kurth, Methuen treasurer, J. Leroy Wood  
 Methuen executive councilor Rolf C. Norris Methuen, legisla-  
 tive councilor Nicandro F. DeCesare, Methuen public rela-  
 tions councilor Harold R. Kurth, Methuen

Essex South — President, Leonard F. Box Beverly vice-  
 president Alexander Kotarski, Peabody, secretary, Henry D.  
 Stebbins, Marblehead treasurer Andrew Nichols III Dan-  
 vers legislative councilor Loring Grimes, Swampscott public  
 relations councilor, Bernard Appel, Lynn executive councilor  
 Walter G. Phippen Salem.

Franklin — President John B. Temple, Shelburne Falls  
 vice president Lawrence R. Dame, Greenfield secretary and  
 treasurer Harry L. Craft Ashfield, public relations councilor  
 Howard M. Kemp Greenfield

Hampden — President Arthur F. G. Edgelow, Springfield  
 vice president, Robert Hildreth, Westfield secretary and  
 treasurer George C. Steele West Springfield executive coun-  
 cilor Archibald J. Douglas Westfield legislative councilor  
 Arthur Rordan Indian Orchard public relations councilor  
 Fredric Hagler Springfield

Hampshire — President, John J. Curtan Northampton  
 vice-president, Edward J. Maxwell Northampton, secretary  
 and treasurer F. Mary P. Snook, Worthington librarian  
 Abbie M. O'Keefe, Northampton executive councilor Henry  
 A. Taddell Belchertown legislative councilor, Lawrence N.  
 Durgin, Amherst public relations councilor Joseph R. Hobbs,  
 Williamsburg

Middlesex East — President Daniel L. Joyce, Woburn  
 vice president, Milton J. Quinn, Winchester secretary, Roy W.  
 Layton Melrose treasurer Albert E. Small, Winchester  
 librarian Angelo L. Maletta, Winchester public relations  
 councilor Milton J. Quinn Winchester

Middlesex North — President, C. Stoyke Baker Lowell  
 vice-president James Y. Rodger Lowell secretary Brendan  
 D. Lenhey Lowell, treasurer Mason D. Bryant, Lowell  
 executive councilor William M. Collins Lowell, legislative  
 councilor A. Warren Stearns Lowell public relations coun-  
 cilor Samuel Dibbins, Lowell.

Middlesex South — President John F. Casey Allston  
 vice-president, Arthur M. Jackson, Everett secretary Alex-  
 ander A. Levi, Newton, treasurer Fabian Packard Belmont  
 orator Vlado A. Getting Belmont, legislative councilor  
 Kenneth J. Tillotson, Belmont public relations councilor  
 Ralph H. Wells Lexington executive councilor Harold G.  
 Giddings, Newton.

Norfolk — President, Carl Bearse, Newton vice president  
 George W. Papen Brookline secretary, Basil L. Barton West  
 Roxbury treasurer Frederick Reis, Jamaica Plain executive  
 councilor Charles J. E. Kichham Jamaica Plain, legislative  
 councilor Solomon L. Skvirsky, Chestnut Hill public relations  
 councilor Dean S. Luce, Canton

Norfolk South — President Robert L. Cook, Quincy  
 vice president, George D. Dalton Wollaston, secretary  
 Ebenezer K. Jenkins Braintree, treasurer Francis G. King  
 North Quincy librarian, Ebenezer K. Jenkins, Braintree  
 public relations councilor, Henry A. Robinson Hingham  
 executive councilor Fred A. Bartlett Hingham legislative  
 councilor David L. Belding Hingham

Plymouth — President, Ralph C. McLeod Brockton  
 vice-president, Sterling A. McLean Middleboro secretary  
 Samuel Gale Brockton treasurer Alton L. Hurlbut, East  
 Bridgewater librarian John H. Weller Bridgewater execu-  
 tive councilor, George A. Moore Brockton public relations  
 councilor Charles D. McCann, Brockton legislative councilor  
 Alfred L. Duncombe Brockton

**Suffolk** — *President*, Charles C Lund, Boston, *vice-president*, Hollis L Albright, Boston, *secretary*, Charles G Shedd, Boston, *treasurer*, Richard S Eustis, Boston, *executive councilor*, Alexander J A Campbell, Boston, *legislative councilor*, William E Browne, Boston, *public relations councilor*, Howard F Root, Boston

**Worcester** — *President*, Frank B Carr, Worcester, *vice-president*, John J Dumphy, Worcester, *secretary*, Julius J Tegelberg, Worcester, *treasurer*, Arthur D Ward, Worcester, *librarian*, John Fallon, Worcester, *executive councilor*,

Bancroft C Wheeler, Worcester, *legislative councilor*, George R Dunlop, Worcester, *public relations councilor*, Nicholas S. Scarcello, Worcester

**Worcester North** — *President*, Jesse C. Hales, Gardner, *vice-president*, Donald B Cheetham, Athol, *secretary*, James G Simmons, Fitchburg, *treasurer*, Frederick H Thompson, Jr, Fitchburg, *executive and legislative councilor*, John J Curley, Leominster, *public relations councilor*, James V McHugh, Leominster

### ADMISSIONS RECORDED FROM MAY 22, 1946 TO MAY 22, 1947 -

YEAR OF ADMISSION	NAME AND RESIDENCE	MEDICAL SCHOOL
1946	Abele, Virgil, Framingham	Middlesex
1946	Abriel, Albert G, Medford Hillside	Boston University
1946	Adams, Crawford W, Malden	Boston University
1946	Adams, Lambi N, Worcester	Hahnemann Medical College
1947	Adler, Morris H, Newton	University of Vienna
1946	*Adzgian, Nazareth, Newton Lower Falls	Tufts
1947	Albano, Peter R, Great Barrington	Middlesex
1946	Albert, Harold S, Boston	McGill University
1946	Alexander, Eben, Jr, Brookline	Harvard
1947	Alexander, Fred, Boston	University of Maryland
1946	Alford, Hyman, Dorchester	Tufts
1946	Amerena, John P, Randolph	Middlesex
1946	*Anderson, Albert B, Cambridge	Harvard
1947	Anton, Harry J, Three Rivers	University of Vermont
1947	Appel, John F, Holyoke	Jefferson Medical College
1946	Arnone, William H, Brockton	New York University
1947	Arthurs, Alexander T, Somerville	Middlesex
1946	*Ayres, John C, Brighton	Boston University
1946	Bailey, David B, Lowell	Tufts
1947	Baker, Donald V, Uxbridge	Harvard
1947	Baldry, George S, Quincy	University of Manitoba
1946	Ballin, Ludwig, South Braintree	University of Munich
1946	Bartol, George, Wellesley Hills	University of Pennsylvania
1947	Barton, David J, Everett	Johns Hopkins University
1946	*Bassett, Gardner G, Brockton	Harvard
1947	Bautze, Frank A, Baldwinsville	Harvard
1946	Baver, Charles L, Stockbridge	Middlesex
1947	Beakey, John F, Cambridge	Tufts
1946	Bedrick, Morton, Fall River	Harvard
1947	Beer, Freda S, Waltham	Friedrich-Wilhelm University
1946	Benoit, Noe N, Millbury	Tufts
1946	Berk, Morton S, Newton Centre	Boston University
1947	Berry, Francis D, Milford	Tufts
1947	Bicchieri, N Anthony, Roslindale	University of London
1947	Binder, Abraham A, Brookline	Boston University
1947	Blechman, Benjamin, Lowell	Leipzig University
1946	Bluestein, Louis L, Hyde Park	Middlesex
1947	Blute, James F, Jr, Watertown	Harvard
1947	Boardman, Donnell W, Acton	Columbia University
1947	Bolino, Armand V, Lynn	Kansas City University of Physicians and Surgeons
1946	Bourne, George C, Hyannis	Tufts
1946	Bragdon, Joseph H, Dedham	Columbia University
1946	Breed, Frederic B, Gloucester	Harvard
1947	*Bresnick, Elliott, Brookline	Tufts
1947	Brewster, Henry H, Milton	Harvard
1947	Bridges, William C, Newton Centre	Yale
1946	Briggs, Bernard D, Stoneham	College of Medical Evangelists
1947	Brochu, Charles E, Webster	Georgetown University
1946	Brooks, Eugene F, Wrentham	Middlesex
1947	Brougham, Milton F, Wollaston	Harvard
1946	Brown, Chester W, Worcester	University of Rochester
1946	Brown, Harold F, Wellesley Hills	Tufts
1947	Brown, Robert H, Foxboro	Harvard
1946	Bruno, Salvatore J, Medford	New York Medical College
1947	Bryan, Burton D, Fall River	University of Vermont
1946	Buckley, William R, Medford	Boston University
1946	Burden, Charles N, Taunton	Tufts
1947	Burger, Harold, New Bedford	Boston University
1947	Burnett, Charles H, Newtonville	University of Colorado
1946	*Bush, James F, Monson	Tufts
1946	*Butman, Douglas E., Waltham	Harvard
1947	Byrne, John J, Weston	Harvard
1947	Cahan, Alvin M, Boston	Cornell University
1947	Campbell, Elmore M, Dorchester	Tufts

1947	Campbell, James B. Jamaica Plain	Harvard
1946	Capodilupo, Graziano A., Boston	Middlesex
1946	Caradonna, Matteo, Everett	Middlesex
1947	Cardillo, Edward M., Everett	Middlesex
1946	*Carr, Francis J., Somerville	Boston University
1946	Carroll, John J., Dedham	Tufts
1946	Carter, Barbara F., Boston	Tufts
1946	*Carter Sidney Reading	Boston University
1946	Castel, Arthur L., Great Barrington	University of Rostock
1946	Cavanaugh Thomas E. Jr. West Springfield	Georgetown University
1946	Ceplikas, Thomas A. North Andover	Tufts
1947	Chalmers Thomas C., Jr., Cambridge	Columbia University
1947	Chasen William H., Roslindale	University of Lausanne
1947	Cheney Roger H., Springfield	University of Pennsylvania
1946	*Chretien Thomas E., Auburndale	Tufts
1947	Clancy George F. Marlboro	Georgetown University
1947	Clary, Robert V. Cambridge	Harvard
1946	Cinton Marshall Jr. Wellesley	University of Buffalo
1947	Coburn Morton B. New York	Middlesex
1946	Cohen, Sidney, Boston	Harvard
1946	Collins, Gerald M. Hingham	Boston University
1946	*Colozzi, Anthony E. Lexington	Boston University
1947	Conlan, William P. Holbrook	Boston University
1947	Connors Raymond J., Fall River	Harvard
1946	*Covell, Lester L., Woburn	Tufts
1946	Curley, George A., Mattapan	College of Physicians and Surgeons Boston
1947	Dalel Saul S. West Roxbury	Louisiana State University
1947	Daly, Bernard J., Lawrence	Georgetown University
1946	*Dana, Jacob B., Brighton	Boston University
1947	D'Avanzo, Charles S., West Springfield	New York Medical College
1946	David, Lloyd G., Lowell	Tufts
1947	Davis, Jean P., Wellesley	Yale
1947	Deacon, Walter E., South Duxbury	Tufts
1947	Dean, Michael A., Millville	Tufts
1946	Deering, George E., Worcester	Harvard
1946	Dennehy, Timothy J. Chestnut Hill	Georgetown University
1946	Diamond Morris Athol	University of Vienna
1947	Diamond, Charles A., West Springfield	New York Medical College
1946	Dine, Robert F., Brookline	Yale
1946	Donoghue, William F. Jr. Springfield	Tufts
1946	Doret, Stanley A., Greenfield	Tufts
1946	*Dorgan Joseph A., Brighton	Tufts
1946	Dorman, Daniel B., Pittsfield	Harvard
1947	Dove, David, Beverly	Harvard
1947	Driscoll, Cornelius J. Danvers	Georgetown University
1946	Ehrenberg Ruth, Northester	University of Berlin
1947	Eichwald Ernst J., North Weymouth	Albert Ludwig University
1946	*Emerson George F. South Weymouth	Harvard
1946	Emerson, Kendall Jr. Brookline	Harvard
1946	England, Albert C., Jr. Brookline	Harvard
1947	Farrand, Robert E., Saugus	Tufts
1947	Feldman, Joseph D., Boston	Long Island College of Medicine
1946	Fercaten, Morris East Brewster	Tufts
1947	Fisher, H. Bernard Dorchester	Tufts
1947	Fitzgerald James A. Brookline	Harvard
1947	Fleming, William L. Newtonville	Vanderbilt University
1947	Fletcher Kenneth S. Jr. Chicopee Falls	Boston University
1946	Ford Richard, West Roxbury	Harvard
1947	Foster George B., Jr. Cambridge	Jefferson Medical College
1946	Fox, Henry M., Wellesley Hills	Johns Hopkins University
1946	Frechette, Alfred L., Westwood	University of Vermont
1946	*French Gordon N. Newton Centre	Tufts
1947	Freni D. Richard Swampscott	Tufts
1947	Fryer Julius W., Danvers	University of Vienna
1947	Garland, Donald M., East Braintree	Tufts
1946	Gellman Raymond, Springfield	Tufts
1947	Gellis Sydney S., Cambridge	Harvard
1946	Gesing Emil J. Lawrence	Kansas City University of Physicians and Surgeons
1946	*Gevart, Frederic C., Jr., Boston	Columbia University
1946	Gianturco, Nicholas D., East Boston	Middlesex
1947	Glicklich Earl A., Brighton	University of Cincinnati
1947	Glickman, Abraham J. Dorchester	University of St. Vladimir
1946	Goldberg M. Milton, Melrose	Tufts
1946	Golden Isaac, Chelsea	Middlesex
1946	Goldfarb Simon L., Northampton	University of Milan
1946	*Goldson Robert J., Mattapan	Georgetown University
1947	Goodstone, Samuel B., Plymouth	Harvard
1946	Gorday Walter J. Harvard	Tufts
1946	Gould Maxwell E. Worcester	Middlesex
1947	Graham John B. Newton Centre	Harvard
1946	Grant, W. Morton Winchester	Harvard



1946	Groden, Harold M, Cambridge	Tufts
1947	Grossman, Myer J, Athol	Middlesex
1946	Grover, Morris L, Springfield	Tufts
1947	Guccione, I Joseph, Roslindale	Middlesex
1947	Gucker, Thomas, Brookline	University of Pennsylvania
1946	Guild, Sherley A, Grafton	Tufts
1947	*Guterman, Burte, Worcester	Washington University
1947	Ham, Donald P, Greenfield	Boston University
1947	*Hanchett, Richard B, Auburndale	Tufts
1946	Harris, Oliver J, Boston	Tufts
1947	Haselhuhn, Donald H, Springfield	Tufts
1947	Hasenbush, Lester L, Dorchester	Johns Hopkins University
1946	Hastings, Nelson, Brookline	Harvard
1946	Hawn, Clinton V, Cambridge	Harvard
1946	Hayden, Charles G, Brookline	University of Minnesota
1946	Hecht, Paul L, Braintree	University of Freiburg
1947	Heifetz, Frank M, Lowell	Tufts
1946	Helman, Milton E, Chelsea	Boston University
1947	Hepburn, James P, Milton	Tufts
1946	Hermanson, Robert H, Brookline	Tufts
1946	Hill, Allen M, Beverly	University of Rochester
1946	Hinton, Elmer E, Boston	University of Kansas
1946	Hirsch, Lawrence S, Framingham	Middlesex
1946	Hoffman, John L, Cambridge	University of Buffalo
1947	Hormell, Robert S, Melrose	Harvard
1946	*Horwitz, William H, Belmont	Johns Hopkins University
1947	Hunter, John J, Cambridge	Tufts
1947	*Hunter, Richard E, Worcester	Boston University
1946	*Irving, Eliot S, Newton Highlands	Long Island College of Medicine
1946	*Isaacson, Philip A, Fitchburg	Dalhousie University
1947	Itkin, Irving H, Worcester	Indiana University
1946	Jaslow, Irwin A, New Bedford	Tufts
1946	Jewett, Everett P, Jr, Worcester	Tufts
1946	Jolliffe, Leslie S, Andover	Queen's University
1947	Jonas, Norman W, Pocasset	Chicago Medical School
1947	Judson, Harry E, Pittsfield	Syracuse University
1947	Kagan, Samuel, Brookline	Midwest Medical College
1946	Kaldeck, Robert, Lowell	University of Vienna
1946	Kaldeck, Rudolph, Dorchester	University of Vienna
1946	*Kaplan, Melvin S, Wellfleet	Albany Medical College
1947	Karpati, Oscar, Brookline	Royal Hungarian University
1946	Karpawich, Peter P, Worcester	Hahnemann Medical College
1946	Kaufmann, William, Holyoke	University of Geneva
1946	Kelley, Thomas F, Brookline	Boston University
1946	*Kelly, Arthur N, Waltham	Tufts
1946	Kennan, Fred J, Boston	Tufts
1946	Kennedy, Arthur P, Lowell	Tufts
1946	Kickham, Edward F, Brookline	Tufts
1946	Kilgore, Philip E, Lynn	Tufts
1946	Killam, Arthur R, Winchester	Boston University
1946	King, Myron N, Winthrop	University of Vermont
1946	Klestadt, Walter D, Fall River	University of Munich
1947	Knapp, Allen H, Quincy	Yale
1947	Krasner, George D, Quincy	University of Basel
1947	Lahey, Philip J, Worcester	Tufts
1946	Lamb, Marshall A, Winchendon	Tufts
1946	Larchez, Albert R, South Hamilton	Boston University
1946	Larcom, Rodney C, Jr, Dedham	Harvard
1946	Larreau, Henry R, Spencer	Boston University
1946	LaVigne, Richard J, Worcester	Tufts
1946	Lavoie, Robert J, Worcester	Hahnemann Medical College
1947	Leani, Aldo, Springfield	University of Vermont
1947	Leavitt, Joseph S, Malden	University of Lausanne
1946	Lenson, Norman, New York	Tufts
1947	Lent, Sylvester M, Hinsdale	Middlesex
1947	Leonard, Field C, Brookline	Harvard
1946	Lepreau, Frank J, Jr, New Bedford	Harvard
1946	Levenson, Herbert M, Brighton	Boston University
1946	Levine, Albert, Mattapan	Middlesex
1946	*Levine, Reevan I, Dorchester	Tufts
1946	Levinson, Leon, Newton Highlands	Tufts
1946	Levreault, Gerald V, Newton Centre	Tufts
1946	Lewenstein, Howard J, Brookline	Tufts
1946	*Lewis, Herbert D, West Newton	Tufts
1947	Lightman, Mashe U L, Lowell	Harvard
1947	Lipman, Daniel G, Lynn	Middlesex
1947	Livingstone, Robert G, Boston	Middlesex
1947	Lord, William J, Great Barrington	Harvard
1946	Loth, Eric C, Jamaica Plain	Albany Medical College
1946	Luongo, Angelo J, Revere	Middlesex
1946	Lydon, Roy T, Norwood	Middlesex
		Tufts

1947	Lyle, Walter I., Warcham	Middlesex
1946	Lynch, Alice D., Dorchester	Tufts
1947	Lyons, Melvin A., Dorchester	Boston University
1947	Magwood, Robert W. Lynn	Tufts
1946	Maislen, Arthur A., Pittsfield	University of Vermont
1946	Malloof, Emil G., West Roxbury	Middlesex
1946	Manconi, Salvatore A., Revere	Boston University
1947	Mandeville, Ernest A., Holyoke	Tufts
1947	Manella, Samuel R., New Bedford	Boston University
1947	Mann, Harold E., Dorchester	University of Pennsylvania
1947	Masterson, James H., Worcester	Tufts
1947	Matloff, Jacob, Brighton	Boston University
1947	Matz, Myron H., Dorchester	University of Minnesota
1947	McArdle, John J., Lawrence	New York University
1946	McArthur, Janet W., Minnesota	Northwestern University
1946	McCombs, Robert P., Brookline	University of Pennsylvania
1946	*McDonough, Walter J., Brighton	St. Louis University
1947	McIver, John M., Hingham	Boston University
1946	McKeigue, John E., Boston	Jefferson Medical College
1947	McKenna, Harold J., Fall River	Creighton University
1946	McLinnis, Peter F., Lawrence	Middlesex
1946	McLaughlin, Laurence S., Woburn	Tufts
1947	Merola, Joseph F., Waltham	Middlesex
1947	Merrick, Edward M., Milton	Middlesex
1947	Metcalf, Roger G., Southbridge	University of Rochester
1946	Meyer, Robert R., Newton Centre	Tufts
1947	Michell, Leon G., Lynn	Johns Hopkins University
1947	Middlebrook, Gardner, New York	Harvard
1946	Mullen, Morris H., North Weymouth	Middlesex
1946	Miller, Harold, Chelsea	Midwest Medical College
1947	Miller, Harold I., Dorchester	Boston University
1947	Miller, Julius Y., Allston	Tufts
1946	Mitchell, Ralph J., Vineyard Haven	Vanderbilt University
1946	Monaghan, Leo B., Concord	Tufts
1946	Moore, Kenneth T., Hanover	Hahnemann Medical College
1947	Moriarty, Daniel J., Worcester	University of Vermont
1947	Morris, Lloyd E., Longmeadow	Ohio State University
1946	Morrison, Benjamin G., Northampton	Long Island College of Medicine
1946	Morrison, Herbert S., Brookline	McGill University
1947	Morrison, John L., Waltham	University of Pennsylvania
1946	Morae, Lawrence S., Brookline	Tufts
1946	Mosher, Henry A., Belmont	Northwestern University
1947	Mossig, William, Springfield	New York University
1947	Mucci, Alfred C., Somerville	Middlesex
1947	Mulvey, William A., Gloucester	Georgetown
1946	Myerson, Paul G., Boston	Harvard
1946	Naumann, Hans N., Taunton	Berlin University
1946	*Nereo, Oswaldo A., Quincy	Boston University
1947	Nochimow, Eliezer, New Bedford	Midwest Medical College
1946	O'Brien, Joseph A., Dorchester	Tufts
1947	O'Brien, Paul A., Winthrop	Tufts
1946	O'Brien, Paul I., Dorchester	Tufts
1946	O'Connell, William T., Roslindale	Tufts
1947	O'Day, John J., Norwood	Tufts
1946	O'Hara, John L., Newton	Tufts
1946	*Olive, George M., Jr., Belmont	Tufts
1947	Orchard, Norris G., South Harwich	Johns Hopkins University
1946	Osborne, Melvin P., Newton Highlands	Harvard
1947	O'Shea, James A., Lawrence	Long Island College of Medicine
1946	Owen, Charles A., Pittsfield	Tufts
1947	Pandolino, Joseph E., Boston	Tufts
1946	Park, Irving H., Brookline	Middlesex
1946	Parnes, Jacob, Leominster	University of Prague
1946	Paull, Thomas, Boston	Harvard
1946	*Pavlo, Irving L., Cambridge	Harvard
1946	*Pennell, Walter J., Winchester	Harvard
1946	*Peretsman, Jacob, Somerville	Tufts
1946	*Perrone, S., Joseph, Worcester	Tufts
1947	*Pier, Arthur S., Jr., Milton	Harvard
1946	Pipi, John, East Boston	Middlesex
1947	Pirone, Francis A., Lynn	Tufts
1946	Powers, Hazel C. K., Boston	Middlesex
1946	Powers, Joseph W., Roxbury	Kansas City University of Physicians and Surgeons
1947	Powers, William J., Jr., Sharon	Tufts
1946	Preacott, Blake D., Connecticut	Middlesex
1947	Price, William B., Roxbury	Mcharry Medical College
1946	Putnam, Henry M., Westwood	Harvard
1946	Putnam, Robert M., Plymouth	McGill University
1947	Quinn, Edward M., Jr., Lowell	Tufts
1946	Radcliffe, James Jr., New Bedford	Yale
1946	Radovsky, Everett S., Fall River	Middlesex

1946	Record, Eugene E , Boston	McGill University
1946	Reder, Benjamin,, Fall River	Boston University
1946	*Regan, John E , Roslindale	Tufts
1946	Riccardi, Louis S , Marlboro	Middlesex
1946	Rizzo, Nicholas D , Brookline	Boston University
1946	Robinson, George E , Fall River	College of Physicians and Surgeons, Boston
1947	Robinson, Henry S , Somerville	Kansas City University of Physicians and Surgeons
1946	Roodin, Harry, Roxbury	College of Physicians and Surgeons, Boston
1947	Rosen, Abraham E , Worcester	Tufts
1946	Rosmatin, Ernest, Boston	University of Vienna
1947	Rossmann, Benny, Brookline	University of Marburg
1947	*Ruben, Maurice, Dorchester	Boston University
1946	Rupp, John J , Boston	Washington University
1947	Russell, Donald H , Peabody	New York University
1947	Ruzicka, Edwin R , Chestnut Hill	University of Maryland
1946	Ryan, John J , Maryland	Tufts
1947	Saba, Edward, Lowell	Tufts
1946	*Sabino, Anthony W , Newtonville	Tufts
1947	Sanborn, Earl B , New York	Northwestern University
1947	Sarkisian, Sarkis A , Bridgewater	Boston University
1947	Scanlon, Joseph C , Worcester	Boston University
1946	Schwartz, Isaac H , New Bedford	University of Basel
1946	Scivico, Michael W , Worcester	Albany Medical College
1946	Sewall, Edgar F , Jr , Somerville	Tufts
1946	*Shalek, Seymour R , New York	Boston University
1946	Shand, Nathaniel K , Fall River	Middlesex
1947	Shane, Theodore, West Newton	Middlesex
1946	Shapiro, Eli, Roxbury	Middlesex
1947	Sharples, Arthur B , Hyannis	University of Vermont
1946	Sharry, Charles F , Cambridge	Harvard
1947	Shea, Daniel F , Quincy	Georgetown University
1946	Sheehan, John C , Marshfield	Tufts
1947	Sheehan, John F , Worcester	Tufts
1947	Siegel, Robert, New Bedford	Tufts
1946	Sikorsky, Lucy N , Grafton	Boston University
1947	Simoneau, Arthur G , Marlboro	Boston University
1946	Snyder, Eugene, Chicopee Falls	University of Prague
1946	Sommers, Sheldon C , Newton Centre	Harvard
1947	*Sozanski, Julius C , Peabody	Loyola Medical School
1946	Sprague, Marion L , Worcester	College of Medical Evangelists
1947	Stanley, Edith D , Brookline	Temple University
1947	Stanton, Joseph R., Newton	Yale
1947	*Stanton, Richard H , Boston	Harvard
1946	Starr, Steven J , Worcester	Georgetown
1946	Steinberg, Irving H , Northampton	Medical College, State of South Carolina
1946	Steinman, Solomon E , Brighton	Boston University
1947	Stevenson, Stuart S , Boston	Yale
1947	Stone, Chauncey M , Jr , Arlington	Boston University
1946	Strauss, Elliott G , Northampton	Tufts
1947	Strauss, Louis, Dorchester	Middlesex
1947	Sullivan, Arthur P , Quincy	Tufts
1946	Sullivan, Frederick J , Jr , Fall River	Jefferson Medical College
1947	*Sunshine, Samuel, Milton	Middlesex
1946	Swank, Roy L , Newton Highlands	Northwestern University
1946	Swartz, Morris, Dorchester	Boston University
1947	Sweetser, Elliott H , Malden	Boston University
1947	Thompson, Charles A , Newton Highlands	Tufts
1946	*Thompson, Robert C , Swampscott	Syracuse University
1946	Tierney, Thomas M , Brighton	Georgetown
1946	Toppenberg, David R , Melrose	College of Medical Evangelists
1946	*Traina, Salvatore R , East Boston	Tufts
1946	Trnby, William W , Brookline	Harvard
1946	Trodella, George P , Somerville	Tufts
1946	True, Ansel B , East Northfield	Yale
1947	Tucker, Walter I , Boston	Harvard
1946	Tullis, James L , Newton	Duke University
1946	*Vecchione, Felix S , East Boston	Boston University
1946	Viterbi, Achille, Boston	University of Turin
1946	Waite, Harold V M , Easthampton	Middlesex
1946	Warren, Kenneth W , Newton Highlands	Temple University
1946	Webster, Richard C , Jr , Burlington	Harvard
1947	Weinberger, Jerome L , Boston	New York University
1947	Weisman, William S , Mattapan	Middlesex
1946	Welch, C Stuart, Brookline	Tufts
1946	Welch, William J , Taunton	Tufts
1947	Wharton, Russell S , Northampton	University of Arkansas
1946	*White, Malvin F , Cambridge	Yale
1947	Whitman, Elmer L , New Bedford	Tufts
1947	Whitner, Karl R , South Sudbury	Tufts
1946	Wilhelm, Norbert A , Newton Centre	St. Louis University
1946	Williams, Nathan, Allston	Boston University

1947	Willis, Albert W., Lowell	Tufts
1947	Wilson, Franklin L., Stockbridge	Middlesex
1946	Wise, Herman R., Roxbury	Middlesex
1947	Wojciechowski, Anthony A., Webster	Tufts
1946	Wolfe, Louis M., Chelsea	New York University
1947	Woll, Ephraim, Boston	Creighton University
1946	Woods, Francis M., Newton Highlands	Yale University
1946	Woodworth, Clyde R., Peabody	Boston University
1946	Worcester, John, Waban	Tufts
1947	Worthington, Richard V., Framingham	Yale University
1947	Wright, Walter E., Orleans	Cornell University
1947	Wyman, Stanley M., Cambridge	Harvard
1946	York, Richard F., Waban	Middlesex
1947	Zambella, Joseph, Winthrop	Kansas City University of Physicians and Surgeons
1947	Zovickian, Anthony, Watertown	Yale

\*The candidate, after a personal interview was approved by the Committee on Membership and permitted to take an examination before a board of censors

## DEATHS REPORTED FROM MAY 22, 1946 TO MAY 20, 1947

ADMITTED	NAME	PLACE OF DEATH	DATE OF DEATH	AGE
1894	Adams, Charles Sumner	Wollaston	June 13, 1946	76
1916	†Alley, Ernest J.	Billerica	May 23, 1946	72
1911	Almy, Thomas	Fall River	September 9, 1946	63
1894	†Bailey, Marshall H.	Norwell	September 18, 1946	87
1908	Barker, Williston W.	Dorchester	November 26, 1946	64
1925	Bergeron, George G.	Ludlow	September 26, 1946	55
1883	†Bigelow, Enos H.	Framingham	March 13, 1947	91
1903	Boyle, John F.	Lowell	April 25, 1947	76
1942	Burger, Franklyn D.	Wellesley Hills	November 25, 1946	40
1924	Caldicott, Francis S.	Lowell	January 17, 1947	57
1914	Caswell, Bertram H.	West Somerville	April 14, 1947	72
1915	Chandler, Harold B.	West Newton	July 14, 1946	61
1907	Chase, Harrison A.	Brockton	July 23, 1946	69
1886	†Cheever, Clarence A.	Scituate	November 31, 1946	88
1910	Clarke, Joshua W.	Attleboro	March 27, 1947	76
1919	Clute, Howard M.	Boston	September 19, 1946	56
1903	Collins, Richard	Waltham	July 28, 1946	72
1902	Conroy, Arthur C.	Boston	August 18, 1946	76
1909	†Crosbie, Arthur H.	Boston	August 23, 1946	69
1903	Crosby, Leander M.	New York	August 18, 1946	70
1926	Davis, Max	Boston	April 30, 1947	47
1905	Day, Hilbert F.	Cambridge	May 17, 1947	68
1900	†Dennett, Alonzo G.	Lowell	December 11, 1946	91
1932	Djerf, Frederick J.	Fitchburg	July 15, 1946	45
1892	†Dole, Mary P.	Shelburne	March, 1947	84
1903	Dwyer, William J.	Boston	September 30, 1946	63
1905	Ellis, Edward K.	Needham	June 7, 1946	67
1915	Ellison, Daniel A.	Lowell	February 15, 1947	60
1934	Ellis, Evelyn B.	Waban	July 14, 1946	40
1921	Emery, Edward S.	Brookline	March 16, 1947	53
1943	Ewing, Edward H.	Stoughton	March 8, 1947	74
1943	Gigger, Augustus G.	Falmouth	November 27, 1946	68
1891	†Goffrey, Joseph W.	Lynn	November 27, 1946	79
1919	†Grant, Justin F.	Boston	1947	70
1888	†Hare, Charles H.	Boston	January 21, 1947	84
1935	Harpin, Raymond A.	Lynn	August 10, 1946	41
1926	Hayes, Arthur W.	Montague	March 11, 1947	55
1926	†Hayes, Frederick L.	Brookline	July 7, 1946	77
1901	Hills, Charles E.	South Natick	February, 1947	78
1902	Holbrook, Bradbury	Waltham	August 24, 1946	74
1944	Holt, William L.	Amherst	October 18, 1946	68
1919	Howard, Perez B.	Newtonville	1947	71
1908	†Howland, George L.	Jamaica Plain	August 7, 1946	76
1936	Huber, Edward G.	Waban	July 23, 1946	64
1878	Hunt, William O.	North Falmouth	April 19, 1947	93
1895	Hutchinson, Charles M.	Cambridge	November 26, 1946	76
1921	Jennings, John G.	Weston	February 27, 1947	58
1914	†Johnson, Herbert L.	Hadley	December 22, 1946	87
1917	Kane, William V.	Lynn	December 11, 1946	54
1893	Kees, Philip A.	Pittsfield	1946	39
1911	Kelly, William P.	April 15, 1947	76	
1913	Kerrigan, Joseph H.	Miami, Florida	January 3, 1947	61
1930	Kilburn, Ira N.	Springfield	February 3, 1947	62
1900	Kingsley, Frederick	Chestnut Hill	February 1, 1947	73
1900	Kinney, William D.	Osterville	July 12, 1946	—
1925	Landesman, Henry M.	Boston	May 22, 1946	62

1910	Lee, Harry J	Boston	August 7, 1946
1912	Marsden, George	New Bedford	May 20, 1946
1932	McCarthy, Charles K	Webster, Iowa	1945
1924	McNamara, John J	Lowell	November 13, 1946
1926	Meserve, Faith L	Weston	July 19, 1946
1911	Morgan, Charles R	Medford	November 28, 1946
1916	Moulton, Allen T	Boston	November 22, 1946
1932	Musso, George H	Lynn	March 1, 1947
1906	†Noble, Mary G	Roxbury	February 16, 1947
1922	O'Brien, Thomas F	Worcester	September 16, 1946
1919 } 1934 }	O'Dea, Patrick J	Fitchburg	September 25, 1946
1925	O'Halloran, William T	Newton	March 21, 1947
1919	O'Hara, Francis J	North Adams	May 2, 1947
1910	†Overlander, John E	Springfield	May 26, 1946
1896	†Painter, Charles F	Brookline	January 6, 1947
1892	†Patch, William T	—	February 7, 1947
1921	Perkins, George E	Fitchburg	April 1, 1947
1892	†Phelps, John S	Lynn	December 3, 1946
1907	Phillips, Wilson F	Dorchester	January 29, 1947
1884	†Preble, Wallace	Cambridge	February 22, 1947
1910	Pulsifer, Walter H	Whitman	September 26, 1946
1909	†Quest, James F	Boston	May 27, 1946
1907	Reid, Isadore E	Jamaica Plain	August 12, 1946
1896	Richardson, Mark W	—	February 12, 1947
1916 } 1942 }	Roney, Hugh B	Pittsfield	January 8, 1947
1931	Rose, Wilfred A	San Francisco	September 24, 1946
1901	Ryder, George H	Quincy	March 12, 1947
1893	Sargent, Ara N	Salem	August 26, 1946
1917	Sedgley, Frank R	California	February 12, 1947
1929	Shefferd, Jeannette M	—	October 25, 1946
1926	Simmonds, Frederick J	Jamaica Plain	December 6, 1946
1930	Smith, Roswell H	Edgartown	February 12, 1947
1892	†Stacey, Charles F	Maine	July 18, 1946
1909	Stone, George H	Worcester	January 4, 1947
1914	Stone, Henry E	Dorchester	March 31, 1947
1942	Sullivan, Arthur J	Fall River	August 6, 1946
1942	Sulzbach, Wolfgang M	Boston	1946
1905 } 1925 }	†Sylvester, Albie W	Pittsfield	June 20, 1946
1944	Taylor, Lois E	Belchertown	March 21, 1947
1928	Terry, Theodore L	Stow	September 28, 1946
1908	Tighe, Michael A	Lowell	April 8, 1947
1899	†Tilden, Irving N	Mattapoisett	January 29, 1947
1906	Tinkham, Oliver G	Newton	September 10, 1946
1901	Tozier, Charles H	Winchester	January 1, 1947
1910 } 1946 }	Tynan, Joseph P	—	1947

†Retired fellow

Total number of deaths of active fellows	71
Total number of deaths of retired fellows	22

Grand total	93
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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

### CASE 33351

#### PRESENTATION OF CASE

A forty-six-year-old man entered the hospital because of upper abdominal pain.

There was a life-long history of "stomach ache" three or four times a year. Six years before admission the patient suddenly and painlessly vomited over a cupful of red blood. He was put to bed and treated with Amphogel and belladonna and placed on a bland diet. From that time he began to have gnawing epigastric pain every two or three weeks, lasting one or two days at a time. The pain responded readily to milk, to sodium bicarbonate or simply to a stricter adherence to the diet. Three and a half years before admission the pain became worse and failed to respond to the medical regime. X-ray examination of the stomach was said to have shown an ulcer that was "partially blocking the outlet." An operation, probably a gastroenterostomy, was performed with complete relief for a year and a half. Ten months before admission, after a series of family misfortunes, the attacks returned. At that time they were even severer, occurring several times a week and radiating from the epigastrium to the back. Sodium bicarbonate afforded immediate relief. Six months before entry the patient had an attack of "intestinal grippe," with a pain and cramps low in the abdomen, and diarrhea without blood or mucus lasting for a week. The pain in the upper abdomen was subsequently constant, soda affording relief for only twenty minutes at a time. The patient went on a self-imposed milk and egg diet and lost 16 pounds without much benefit. He could not recall specific instances of food aggravating the pain, but had an impression that eating normal meals was deleterious. Throughout that period he never felt nauseated and had noted no change in bowel habits.

Physical examination revealed a thin patient, who complained of gnawing epigastric and back pain until relieved by milk. The heart and lungs were normal. A vertical scar occupied the midline in the epigastrium. The epigastric region was slightly tender.

The temperature was 99.5°F, the pulse 88, and the respirations 16. The blood pressure was 120 systolic, 74 diastolic.

Examination of the blood disclosed a red-cell count of 4,250,000 and a white-cell count of 14,500, with 80 per cent neutrophils. The urine was normal. The stools gave a ++ reaction for blood.

On fluoroscopic examination, the stomach was seen to be filled with a large amount of residual food. Along the lesser curve there was a large area of rigidity, with an ulcer crater 2 cm. in depth and 3 cm. in diameter within which there was a filling defect (Fig. 1). The lesser curvature, from a distance of about 2 cm. above the ulcer down to the pylorus, was rigid and shortened. Insufficient barium passed into the duodenum to fill out the duodenal bulb to a normal contour. No barium left the stomach by way of an anastomosis.

A fasting gastric aspiration failed to produce free acid, which was present after the administration of histamine, however.

The patient was kept virtually free of pain by hourly feedings. The temperature and white-cell count fell to normal. The morning gastric residual fluid was reduced from 300 to 75 cc. during the first week. On the seventeenth day gastroscopy revealed a constantly deformed and rigid-appearing angulus whose outline was irregular and slightly nodular. No peristalsis was visible. The ulceration seen at fluoroscopy was out of the range of the gastroscopist.

Three days later an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR. RICHARD SCHATZKI: I shall reverse the customary procedure and start with the x-ray films. That is my usual approach to a case, although I have the history in the back of my mind while discussing the films. The record gives an adequate description of what is seen on the films. There is a crater. One thing that I cannot see but that the fluoroscopist apparently saw is the pylorus, unless it is this area, which would mean that the crater extended all the way to the pylorus. The lesion is characterized by a large crater that differs from the usual crater in that it contains a filling defect. The rigidity described in the record is not visible on the film. The shortening of the lesser as compared to the greater curvature can be seen. Another point, not mentioned in the record, is that the gastric folds converge to this crater. That does not help in differential diagnosis, however, because we have seen too many cancers with converging folds. Some of the folds reach the crater, but others do not quite reach it. That may be of significance.

The differential diagnosis, of course, is between benign and malignant ulcer. I might say that if the roentgenologist can be of any help in the differential diagnosis it is in the type of case in which he can see a tumor that has become ulcerated. The ulceration may be the leading roentgenologic sign, but by careful examination the tumor that has ulcerated and surrounded the ulcer may be demon-

strated. In such a case the roentgenologist is helpful because he can make a flat-footed diagnosis of cancer. There are other cases in which the lesion has the characteristic appearance of what we learned in school to be peptic ulcer of the stomach. In a case like the one under discussion the roentgenologist can say that the ulcer is macroscopically benign but cannot say that the lesion is not malignant.

This may be seen in the ulcerative infiltrating type of cancer. Another reason is this peculiar defect in the crater. After having looked at the defect for some time I decided that I still did not know what it was. I thought of a polypoid tumor protruding into the lumen, which I cannot remember ever having seen and which I do not believe this defect represented. I am certainly not able to say

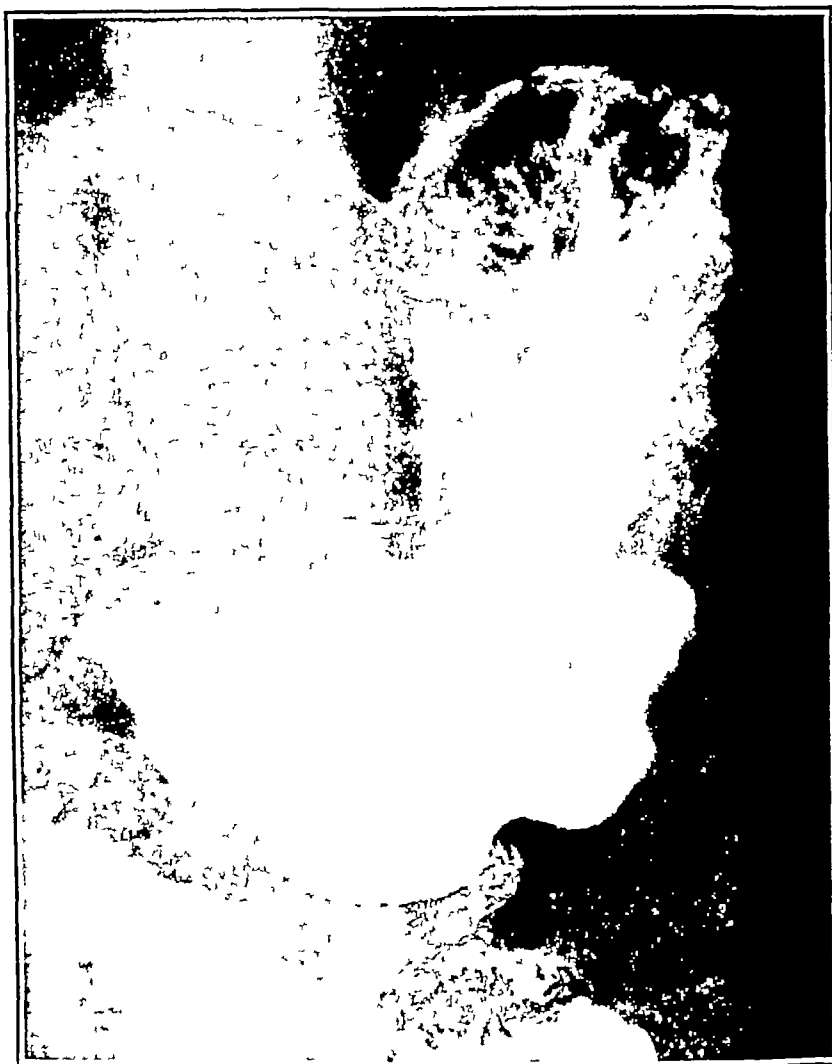


FIGURE 1

nant histologically. I shall not go into statistics regarding how many of these lesions turn out to be cancer on microscopical examination. A third type of lesion — these are the difficult ones — occurs in cases in which the ulceration is present in an infiltrating cancer. The cancer does not form a real tumor mass but merely a small, nodular irregularity around the crater. In the case under discussion I cannot see anything that I should call a gross polypoid tumor that may have ulcerated. Offhand, my first impression was to call this a grossly benign ulcer from the x-ray point of view. There are a few disturbing facts about such a statement, one of which is that the folds do not quite reach the

whether an anastomosis was present, since none is visible. One reason for its not being visible may be that the anastomosis was closed off, another possibility is that the operation three and a half years before entry was not a gastroenterostomy done on the lower pole of the stomach but a pyloroplasty. In that event the appearance of the crater might have had something to do with the operative procedure. There was no history of bleeding in this case to warrant the diagnosis of blood clot. Food in the ulcer may give such an appearance, although the defect seems too constant to be explained on the basis of food. It may be worth while to say a few words about the clinical record

I believe that the history alone in cases of this sort does not indicate the differential diagnosis between benign and malignant ulcers, but it increases the percentage of probability one way or the other. When I started reading the history I had no doubt that the patient had had a benign ulcer in the past, at either the pylorus or the duodenum. The course sounds typical of a classic case of ulcer. Then, in the last year, something happened. The history becomes confusing. If one did not have the first part of the record one might think that this was a case of cancer. The pain was relieved by milk. I do not know how much attention is paid these days to gastric acidity. It can certainly be said that patients with cancer may have a great deal of gastric acid and that patients with ulcer may have no acid at all, although in a large group of cases patients with ulcer have more acid than those with cancer. In a case like the one under discussion the presence or absence of acidity does not make the diagnosis, it merely changes the percentage. This man had some acid after the administration of histamine.

How does the size of the ulcer enter the picture? It does not, as a matter of fact. If there is a large crater, which appears grossly benign, the chances are that histologically it will be benign. The cases in which there is difficulty in the differential diagnosis are those of small ulcers, 1 or 2 cm. in diameter. I shall not discuss the significance of the location of the ulcer in detail and shall say only that a great many ulcerations in the prepyloric areas are cancers and that a great many are benign.

Why, in a given case, does one bother to talk about the differential diagnosis — why not remove the stomach if the treatment of gastric ulcer is definitely surgical? It is true that in practically none of these cases can histologic malignancy be ruled out, but given a lesion that looks grossly benign in a patient who is a poor operative risk, one should be more conservative in treatment. For this reason it is justifiable and essential to make the preoperative diagnosis as exact as possible. In the case in question the chances are that the lesion was grossly benign, but it may have been an ulcerated infiltrated cancer. This is not the type of ulcer that I should entrust to medical treatment.

Dr. BENJAMIN CASTLEMAN: The report of Dr. Schulz was as follows: "The appearance is that of a large gastric ulcer that has more of the criteria of a grossly benign ulcer than of a malignant one. Cancer cannot be ruled out. The area is fixed."

Dr. WELCH, have you any opinion?

Dr. CLAUDE E. WELCH: I should think that it was cancer. If you ask me why, I cannot tell you.

#### CLINICAL DIAGNOSIS

Gastric ulcer  
Gastric carcinoma?

#### DR. SCHATZKI'S DIAGNOSIS

Grossly benign ulcer

#### ANATOMICAL DIAGNOSIS

*Multiple benign peptic ulcers of stomach*

#### PATHOLOGICAL DISCUSSION

Dr. C. J. MIXTER, JR.: This man had had a previous posterior gastroenterostomy, and at operation there was a large mass in the region of the prepyloric area that grossly appeared to be malignant. There was also evidence of an old duodenal ulcer. The duodenum was closely drawn together, so that the acute lesion was really a prepyloric ulcer. Since the lesion appeared to invade the pancreas beneath it, we thought that it was necessary to treat it as a malignant lesion and took out part of the pancreas beneath it.

Dr. CASTLEMAN: The specimen that we received showed a firm, brawny mass in the lower third of the stomach. The fat around it seemed to be porky. When the stomach was opened the center of the mass showed an ulceration about 4 cm. in diameter. We were unable to find anything to correspond to the filling defect. One of the surgeons who saw it said that the base was flat and granular and that there had been no projections from it at the time of operation. There may have been something there when the x-ray film was taken. Just distal to the ulcer was an opening of a gastroenterostomy on the posterior wall, and there was also another ulcerating, rather shallow lesion on the lesser curvature. On microscopical examination the large ulcer was benign, with a base that was made up primarily of the serosal fat. There was practically no stomach left. The other lesion high up on the stomach was also a benign ulcer.

Dr. SCHATZKI: Do you remember how large the upper ulcer was?

Dr. CASTLEMAN: Less than 1 cm. in length and somewhat shallower in depth — I should say, from the microscopical sections, not more than 0.5 cm.

#### CASE 33352

#### PRESENTATION OF CASE

*First admission.* A sixty-one-year-old American-born Irish plumber was admitted to the hospital because of abdominal swelling.

About two months before admission the patient had noticed the onset of a dull abdominal discomfort centering in the epigastric and periumbilical regions. It was a steady, dull pain occurring during the morning or early afternoon and tending to persist throughout the day. It was sometimes precipitated or aggravated by food or activity. There was no particular way to relieve the pain. The patient had also noticed bloating accompanying meals, and for six weeks prior to admission the abdomen had



become increasingly swollen, causing some dyspnea. He began to be constipated a month before admission, the previous bowel habits having been regular. Laxatives had produced daily bowel movements in that period, and the urine had been dark. During the week before admission he noted that the stools were somewhat lighter. Also for several weeks prior to admission he had noticed an increase in his chronic "cigarette cough," with the production of white phlegm, occasionally flecked with blood. He denied vomiting, hematemesis or tarry stools, although at an interview in the Out Patient Department two weeks prior to admission he had admitted vomiting blood some five weeks previously and passing a dark stool. He had not been jaundiced and had had no itching. He had continued to work until a month before admission.

Ten years previously an operation had been performed for a perforated peptic ulcer, without preceding or subsequent gastrointestinal symptoms until the present illness. After the operation the patient had followed a bland diet for five months, and he was then told that he was well. For at least ten years he had been drinking a pint of whisky and six or seven glasses of beer daily. During that time the diet had been fair, with three meals a day, red meat once daily, at least one vegetable and frequently fruit, until about six months before admission, when his appetite had become rather poor and he had begun to skip meals. He had had occasional epistaxis for many years, most recently on two or three occasions after blowing the nose. Also, the ankles had been swollen for about ten years, in association with the development of varicose veins. He denied any history of rheumatic fever or swollen joints.

Physical examination disclosed a well developed, poorly nourished, ruddy-appearing man in no acute distress, with many telangiectases and spiders over the shoulders, anterior upper portion of the chest and the arms. There was questionable icterus of the scleras, and slight injection of the nasal mucosa. The tongue had smooth, red edges. The heart appeared enlarged to the left and right. The apical impulse was 10 cm to the left of the midsternal line in the fifth interspace. The apical first sound was loud and booming. The pulmonic second sound was louder than the aortic. There was a Grade II systolic, roaring murmur heard best in the third and fourth left interspaces and at the apex. The abdomen was greatly distended, with shifting dullness and a fluid wave. The liver was not enlarged to percussion, and neither the liver edge nor the spleen could be felt. External hemorrhoids were visible on rectal examination. There was a slight tremor of the hands, and Dupuytren's contractures of both hands. There was marked edema up to the mid-thigh, and moderate sacral edema. There was brown pigmentation over the lower legs bilaterally.

Examination of the blood revealed a red-cell count of 3,030,000, with 10 gm of hemoglobin, and a white-cell count of 3300, with 69 per cent neutrophils. The urine gave a ++ test for albumin and a ++ test for bile, with rare hyaline casts in the sediment. The stools were guaiac negative. The prothrombin time was 28 seconds - (control, 16 seconds). The total protein was 7.2 gm per 100 cc, with an albumin of 3.0 and a globulin of 4.2 gm (albumin-globulin ratio of 0.7), the nonprotein nitrogen was 22 mg, the cholesterol 170 mg and the vitamin A 0.0 units per 100 cc, and the cephalin-flocculation test was +++ in twenty-four and ++++ in forty-eight hours. The van den Bergh reaction was 1.4 mg per 100 cc direct and 2.2 mg indirect, and the alkaline phosphatase 2.7 units per 100 cc. The blood Hinton reaction was negative.

A gastrointestinal series revealed a small hiatus hernia at the lower end of the esophagus and varices in the esophagus above. The stomach appeared quite normal. Barium passed the pylorus without hesitation, filling the duodenal bulb, which was deformed in a manner characteristic of an old ulcer but within which no active crater could be demonstrated. Chest films showed prominence of the left ventricle and linear areas of atelectasis in both bases. There was elevation of both leaves of the diaphragm.

Mercupurin, with a high-protein, high-carbohydrate, low-fat diet, was administered, and two transfusions were given. Two and a half weeks after admission the total protein was 7.1 gm per 100 cc, with an albumin of 2.3 gm and a globulin of 2.8 gm (albumin-globulin ratio of 0.9), the prothrombin time had dropped to 20 seconds (control, 15 seconds), and the cephalin-flocculation test remained unchanged, as did the van den Bergh reaction. A paracentesis three weeks after admission yielded 8350 cc of cloudy, amber fluid with a specific gravity of 1.012. A bromsulfalein test at that time revealed 44 per cent retention of the dye. In spite of massive doses of vitamin K intravenously, the prothrombin time remained at 20 seconds against a 15-second control. It was believed that this contraindicated a liver biopsy.

A month after admission the temperature suddenly spiked to 103°F, following a shaking chill. The patient had a nosebleed that morning, and he stated that he had been getting blood out of the back of his throat for the past three days. He had a slight cough, no chest pain or dyspnea and no leg or abdominal pain. The throat was slightly injected. A chest film showed linear areas of increased density in the right lower chest. The right leaf of the diaphragm was elevated and somewhat irregular. By that night the temperature had receded, and the patient felt much better. A few days later a cephalin-flocculation test was ± in twenty-four hours and ++ in forty-eight hours, and the thymol turbidity was 5.5 units. The

icterus seemed definitely less. The hemoglobin was up to 13 gm. Ascites, however, seemed to reaccumulate rather rapidly. Five weeks after admission the patient vomited following nausea, although he had had almost nothing by mouth. He had one bowel movement of tarry, black, unformed material and seemed slightly confused, twitching frequently with gross clonic contractions of large muscle groups, but he showed no evidence of shock and the blood pressure and pulse remained steady. Subsequently, he passed two fairly large tarry stools. There was no change in the blood pressure or pulse and no hematemesis. Several transfusions were given, and the stools became brown but were still guaiac positive. There seemed to be little change in the course, and the bleeding had apparently stopped; consequently, the patient was discharged on a strict diet seven weeks after admission.

*Second admission (six weeks later)* During the interim the patient was followed in the Out Patient Department and apparently kept to his diet. He was given Mercupurin, and occasional paracenteses were done. After the last paracentesis he developed a dry cough and pain in the lower abdomen, especially when coughing. He had had a few small hemoptyses during the week prior to admission. He had felt badly, and his appetite had become poor. He suddenly developed a shaking chill, with a subsequent rise of temperature, and he was admitted to the hospital with a temperature of 104.5°F and a blood pressure of 148 systolic, 84 diastolic. He was treated with penicillin and within three days showed great clinical improvement with subsidence of the fever. A paracentesis was performed on the fourth hospital day, yielding 12,700 cc of deep-yellow, opalescent fluid with a specific gravity of 1.004. The patient was subsequently discharged.

*Final admission (two weeks later)* The patient was admitted in a slightly confused state. He stated that about a week before admission his appetite had begun to diminish and that he had started to vomit coffee-grounds material after meals. He was constipated for a week, and when he finally had a bowel movement on the day of admission the stool was copious and brown. He had observed no frank blood in the stools, which had not been clay colored. During that period he had complained of severe heartburn starting in the epigastrium and made worse by food. This pain radiated up to the anterior portion of the chest. Four days prior to admission the abdomen had become tight and swollen, and a physician had performed a paracentesis. The patient was given 4 gm of ammonium chloride daily for a week.

Physical examination was essentially unchanged. Examination of the blood revealed a red-cell count of 3,000,000, with 10 gm. of hemoglobin, and a white-cell count of 8600, with 84 per cent neutrophils, 16 per cent lymphocytes and toxic granulation of

the neutrophils. The urine was normal. The stools were guaiac negative. The carbon dioxide was 20.8 milliequiv per liter, the prothrombin time 33 seconds (control, 20 seconds), the cephalin-flocculation test + in twenty-four and ++ in forty-eight hours, and the total protein 7.0 gm per 100 cc, with 2.5 gm of albumin and 4.5 gm of globulin (an albumin-globulin ratio of 0.55). The nonprotein nitrogen was 52 mg per 100 cc., the chloride 91 milliequiv per liter, and the van den Bergh reaction 3.6 mg per 100 cc direct and 5.4 mg indirect. The patient seemed to improve temporarily, but on the tenth hospital day he began vomiting large amounts of guaiac-positive, coffee-grounds material. There was some tenderness in the epigastrium, and finally bright-red blood began to appear in the vomitus. Repeated transfusions were given, but to no avail, and the patient died after semicoma and a period of vascular collapse on the fifteenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

*DR VINCENT P. DOLE* This patient presented a group of findings that are classic for cirrhosis of the liver. For this primary diagnosis we are given a history of alcoholism, symptoms of anorexia and epigastric discomfort, findings of varices, ascites and hemorrhoids indicating portal hypertension, spider angiomas, low-grade icterus and laboratory evidence of impaired liver function.

There is nothing in the history to suggest that biliary obstruction, neoplasm, infection or toxic agents damaged the liver. On the other hand, it is probable that the patient suffered from a deficient diet, since the stated intake of whisky and beer contributed over 3000 calories a day to a person reported as appearing poorly nourished. Had this caloric intake been supplemented by an adequate diet, he would surely have been obese. The observation of smooth, red tongue edges suggests deficiency of vitamin B factors.

The findings of cardiac enlargement and murmur require separate consideration. Part of the enlargement seems to have been apparent only and due to a transverse position of the heart from a high diaphragm. Allowing for this, there was possibly sufficient dilatation of the left ventricle to cause functional mitral regurgitation. Deficiency of thiamine may have been contributory. There is also a fair possibility that the patient had coronary-artery disease, an electrocardiogram might have been of interest. In any event, there was no engorgement of the neck or arm veins and presumably no tachycardia to suggest that cardiac failure was a factor in the ascites and leg edema.

The episodes of hemoptysis and fever could have been due to pulmonary infection, collapse or infarction. Tuberculosis is an occasional complication of cirrhosis, but the x-ray films are not suggestive of that diagnosis. Sputum examinations would

nevertheless have been desirable. The best explanation appears to me that of multiple pulmonary infarctions, to which the patient was disposed by thrombosis of congested deep leg veins.

Finally, one is struck by the rather abrupt appearance of severe portal hypertension with intractable ascites and death apparently from a ruptured esophageal varix within about five days. Although such a rapid progression after onset of ascites occurs in uncomplicated cirrhosis, one is nevertheless tempted to speculate on a complicating portal-vein thrombosis. The symptoms of abdominal distress are consistent with such a diagnosis but occur quite often in cirrhosis alone.

I am unable either to establish or to exclude the diagnosis of portal-vein thrombosis and must leave a question to be asked of the pathologist.

#### CLINICAL DIAGNOSES

Cirrhosis of liver, alcoholic type  
Rupture of esophageal varices

#### DR DOLE'S DIAGNOSES

Portal cirrhosis  
Portal-vein thrombosis?  
Multiple pulmonary infarctions

#### ANATOMICAL DIAGNOSES

*Cirrhosis of liver, alcoholic type*  
*Duodenal ulcer, chronic, active, with erosion into pancreaticoduodenal artery*  
Hemorrhage, recent, into intestines, stomach and esophagus  
Esophageal varices?  
Ulcerations of esophagus

#### PATHOLOGICAL DISCUSSION

DR TRACY B MALLORY The primary diagnosis in this case proved, as Dr Dole predicted, to be cirrhosis of the liver. The organ was atrophic, weighing only 1050 gm. Its surface was coarsely granular, the granules ranging from 1 to 3 mm in size, and it was diffusely tough and fibrous.

We found several possible sources for the attacks of gastrointestinal hemorrhage. The gross evidence of varices at the time of post-mortem examination was not impressive, but sections of the esophagus showed collapsed mucosal veins of considerably more than normal diameter. The mucosa of the esophagus, however, revealed numerous shallow

linear ulcerations ascending from the cardia of the stomach for a distance of 10 cm. The epithelial layer had been completely destroyed in many areas, exposing an extensive capillary bed, and these excoriations could have been the source of significant bleeding. Finally, the old ulcer in the duodenum had become reactivated, and there was fresh peptic ulceration. It is quite possible that hemorrhage occurred at various times from all three of these factors. At autopsy the entire gastrointestinal tract from stomach to rectum contained blood. The spleen was only slightly enlarged, weighing 300 gm. In patients with extensive hemorrhage just before death, however, the spleen often shrinks rapidly, and it is probable that it was considerably larger during life.

We found no thrombosis in the portal system. The lungs were somewhat collapsed and markedly edematous.

We believe in this laboratory that portal cirrhosis of the liver can be divided into two types. The first of these follows one or more nonfatal attacks of diffuse necrosis or so-called "atrophy." The second is seen ordinarily only in patients with a history of chronic alcoholism and coincident dietary insufficiency. The latter is very readily recognizable in its diffuse progressive stages by the combination of fatty vacuolization of the liver cells and a peculiar and characteristic form of hyaline degeneration. Both these changes, however, disappear rather quickly under the influence of a high-protein diet. In serial biopsies we have been able to show that the fat has decreased by 50 per cent within a month and has almost entirely gone within two months. Consequently, these pathognomonic signs cannot be expected in a patient who has been under medical treatment for a significant period. In such cases we must rely on other criteria for diagnosis. The best of these is the gross appearance of the organ. In cases that follow subacute atrophy the regeneration is irregular and coarsely nodular, the individual nodules frequently exceeding 1 cm in diameter and sometimes reaching 2 cm. The intervening bands of fibrous tissue are correspondingly wide and coarse. In the alcoholic type of cirrhosis, in contrast, the regeneration is much more diffuse, and the nodules are uniformly small, ranging from 1 to 4 mm in diameter. The liver of this patient was clearly the latter type.

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## HOUSE OF DELEGATES

THE report of the Massachusetts representatives to the June meeting of the House of Delegates of the American Medical Association, which will be presented to the Council of the Society at its October meeting, contains several matters of general interest.

In the first place, it comments on the final report of the committee to consider public relations and the liaison between the American Medical Association and the National Physicians Committee. The committee completely justified co-operation with the National Physicians Committee and recommended a change in the public-relations consultant, Rich Associates. The report was unanimously approved, and the recommendation adopted.

Secondly, the delegates report calls attention to the emphasis throughout the meeting on the importance of the general practitioner to the community and the need for helping him in every way possible. This was brought to a climax when it was voted to hold the December meetings of the House of Delegates in various cities, rather than in Chicago, and to follow each meeting with a two-day scientific exhibit arranged for the sole benefit of the general practitioner. Furthermore, the Council on Medical Education and Hospitals advised that, to promote a resolution previously adopted by the House of Delegates whereby hospitals were urged to establish general-practitioner services, one section of 'Essentials of a Registered Hospital' be revised to read, 'Staff sections, such as medicine, obstetrics, surgery, general practice and so forth, should be organized as may seem wise.' In addition, the Council stated that it did not approve of the habit of some hospitals, particularly those approved for resident training, in limiting staff appointments to physicians who are certified by one of the specialty boards, any physician, it added, who has had the training and experience approximately equivalent to that required for certification should be capable of rendering satisfactory service.

Thirdly, the report places emphasis on an address given by the Secretary of War, Robert P. Patterson. Mr. Patterson outlined briefly a bill (H.R. 3174, S. 1143) designed to promote and enhance the professional standing of the Army Medical Corps, thus placing it on a level equal to that in the best civilian practice. This bill contains the following provisions: an increase in base pay for all medical officers with less than thirty years' service, a 25 per cent increase in base and longevity pay for all officers who are certified as specialists, the appointment of outstanding medical specialists from civilian life to grades above those now permitted, the appointment of four physicians, distinguished respectively in the fields of medicine, surgery, neuropsychiatry and preventive medicine, as professors, with the rank of brigadier or major general, to supervise professional standards, educational programs and the assignment of qualified officers, and the utilization, if necessary, of civilian physi-

cians on a temporary part-time or full-time basis, without regard to Civil Service requirements. In closing, Mr. Patterson stated that the War Department would do everything within its power to establish, maintain and foster a high grade of professional attainment within the Medical Corps and requested support of the legislation and the program in general.

At the final session of the House of Delegates, Dr. R. L. Sensenich, of South Bend, Indiana, was made president-elect, and Dr. E. J. McCormick, of Toledo, Ohio, was appointed a member of the Board of Trustees. The annual meetings of the Association in 1948 and 1949 will be held in Chicago and Atlantic City, respectively.

## TOXOPLASMOSIS

THE occurrence of cases of human toxoplasmosis in widely separated areas<sup>1, 2</sup> and a recent report of the results of tests for neutralizing antibodies in human serums<sup>3</sup> help to emphasize the increasing medical importance of this parasitic disease. The recognized types of toxoplasmosis include congenital encephalitis and hydrocephalus in infants, acute encephalitis in older children, acute febrile disease in adults resembling typhus or spotted fever and latent infection in adults detectable only by the presence of neutralizing antibodies in the serum. The clinical and laboratory diagnosis of such a protean disease poses an exacting problem.

One gains the impression from the published cases that the majority of infections are fatal, but several recoveries from acute infections have been reported.<sup>4, 5</sup> Moreover, the detection of neutralizing antibodies in the serums of mothers giving birth to infected infants<sup>3</sup> and also in the serums of persons in a random sample<sup>6</sup> suggests a carrier stage of the infection or recovery from an acute phase of the disease.

Although the clinical signs and symptoms in acute cases of toxoplasmosis are not specific, the outstanding basic lesions in the fetus, in infants and in older children are caused by the affinity of the parasites for the central nervous system. This involvement leads to hydrocephalus, cerebral calcification, encephalitis, mental retardation, convul-

sions and chorioretinitis. In adults, the parasites are more widely scattered in the viscera. Whether or not density of parasitization in adults determines the range of intensity of the infection from latency to acute fatal disease is not known. Nevertheless, an awareness of the inherent diagnostic difficulties in the different age groups is necessary if a specific diagnosis is to be made.

The occurrence of hydrocephalus, intracerebral calcification or chorioretinitis in children should suggest the possibility of toxoplasmosis. To verify the presumptive clinical diagnosis, serologic tests are available and animal tests can be performed with biopsy material, tissues, exudates and sputum.

Two serologic tests, the neutralization<sup>7</sup> and the complement-fixation<sup>8</sup> test, have been devised for the detection of antibodies to *Toxoplasma*. These tests are of value in determining both acute and latent infections. The neutralization test has been used most widely for surveys and for the diagnosis of acute infections. Although evidence has been presented to show that the absence of neutralizing antibodies in the serums of patients with chorioretinitis does not rule out toxoplasmic infection,<sup>9</sup> the test as used by the Minnesota Department of Health gave 163 positive reactions with serum from 761 patients.<sup>3</sup> The heat lability of the neutralizing antibody made it necessary for the Minnesota group to use serums stored under special conditions when fresh specimens could not be obtained. In the St. Louis survey, positive results were obtained with serums from persons giving no previous history of illness identifiable as toxoplasmosis.<sup>6</sup> The divergence of these results suggests some nonspecificity and this possibility should be clarified to determine whether false-positive reactions occur with sufficient frequency to nullify the value of the test. Obviously this necessitates wide application in hospital and field surveys. The complement-fixation test,<sup>8</sup> devised by Warren and Sabin, appears of value only in acute infections, for the test becomes negative after the acute stage has subsided in experimental animals.

The inoculation of animals, particularly of white mice, guinea pigs and rabbits, with material from patients is of distinct value in attempting to isolate *Toxoplasma*.<sup>10</sup> These animals are highly susceptible

to this organism, and although suitable material for inoculation cannot always be obtained from patients, every effort should be made to isolate the organisms from patients with acute disease and with positive neutralization tests

The serologic and animal-inoculation tests serve a twofold purpose each extension of the former provides further evidence of their evaluation, and the development of toxoplasmosis in the animals serves to confirm the clinical diagnosis

In the past, identification of the parasites in tissues has been difficult, primarily because of inadequate fixation and staining and because other parasites, such as Encephalitozoon, Sarcocystis and intracellular tissue stages of *Trypanosoma cruzi* and species of *Leishmania*, bear some morphologic resemblance to *Toxoplasma*. The use of proper fixatives<sup>10, 11</sup> and subsequent staining with polychrome stains yield films or sections in which *Toxoplasma* can be identified

Although the epidemiology and mode of transmission of human toxoplasmosis have not been explained, a wide variety of wild and domestic animals and birds are susceptible to spontaneous infection with species of *Toxoplasma*<sup>12</sup>. Little is known about the specific relation of parasites from animal and human sources. Likewise, the role of animal infections as reservoirs for human infection is unknown whether the parasites are transmissible mechanically from one host to another, by contamination of food and water or by the bite of arthropod vectors

Since no drugs or antibiotics have been found that produce radical cures of acute infections due to *Toxoplasma*, chemotherapeutic studies are needed to search for a drug that will penetrate the host cells and destroy the parasites

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## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Lowell	Sept. 5	Albert H. Brewster
Salem	Sept. 8	Paul W. Hugenberger
Greenfield	Sept. 8	Charles L. Sturdevant
Gardner (Worcester subclinic)	Sept. 9	John W. O'Meara
Haverhill	Sept. 10	William T. Green
Springfield	Sept. 16	Garry deN. Hough Jr.
Pittsfield	Sept. 17	Frank A. Slowick
Brockton	Sept. 18	George W. Van Gorder
Worcester	Sept. 19	John W. O'Meara
Fall River	Sept. 22	David S. Grace
Hyannis	Sept. 25	Paul L. Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments

## BOOK REVIEWS

*Clinical Methods of Neuro-ophthalmologic Examination.* By Alfred Kestenbaum, MD. 8° cloth 384 pp. New York: Grune and Stratton, 1946. \$6.75.

The book covers the field of clinical examination of the eye, the optic pathways and the associated muscles in a clear, orderly manner. The simple diagrams and tables are well integrated with the text. As a review of the clinical methods of ophthalmologic examination the book can be highly recommended. For the clinic it will have to be used with other texts on cases and on experimental research.

*A Manual of Tomography.* By M. Weinreb B.Sc., M.R.C.S. (Eng.), L.R.C.P. (Eng.), F.F.R. (Lond.), D.M.R.E. (Camb). 4°, cloth 270 pp. with 397 illustrations. London: H. K. Lewis and Company Limited 1946. Sh. 45.

Whether this technique is called tomography, laminagraphy, planigraphy, stratiagraphy, vertigraphy or sectography is splitting hairs over historical priorities or the mechanical principles of the equipment with which one happens to be familiar. All these are forms of body-section radiography.

In the twenty-five years since Bocage patented three methods of moving the x-ray tube and the film reciprocally and in the seventeen years since Vallebona published his work on the different principles of rotating the body of the patient on an axis between the tube and the film it is perhaps strange that, except for McDougall's seventy-three page monograph in 1940, no book dealing with the subject of body section radiography has previously appeared. In this country the method has been utilized essentially in only a few centers but abroad it has been embraced enthusiastically in many locations. Among the places where it has become most solidly established is Johannesburg whence comes the present monograph by Weinreb. It is regrettable that this pioneer volume fails dimly to provide guidance to those who, given a little encouragement, might share the author's enthusiasm for the subject.

The book is presented more as an atlas than as a text. The mere printing of three hundred and ninety-seven illustrations on two hundred and seventy pages, however, does not automatically make it a reference book. The author is apparently well aware of this fact, and makes excuses for

himself while he places the responsibility for coming out in print on the editor of the *Clinical Proceedings of Capetown*. The material was evidently gathered together for a lecture given by the author in Capetown in 1944. The text, he admits, has been "cut too severely."

Nevertheless, the book establishes many of the good points of body-section radiography. In the chest field, the technic is seen to be particularly useful in delineating the bronchial tree without the introduction of iodized oil, in discovering cavitations within consolidated pulmonary tissue and in revealing details following thoracoplasty. It may be useful in determining heart sizes in cases in which the cardiac apex is obscured on conventional films by pleurisy or by an epicardial fat pad. Some portions of the spinal column are difficult to visualize on ordinary films, but even the cervico-thoracic region, the lumbosacral articulations, the odontoid process and the atlanto-occipital joints may be shown in good detail on body-section films. Details of congenital scolioses, hemivertebrae, fusions, spondylolyses and fractures may also be revealed. In the skull the method is particularly useful for delineating depressed fractures, the auditory canals, facial fractures and the temporomandibular joints. As extra embellishments, the author has used body-section radiography to outline the aorta in angiocardiograms, to observe the process of healing of fractures of the vertebral bodies, to distinguish traumatic Schmorl's nodes from those associated with adolescent kyphosis and to visualize excretory urograms in infants whose kidneys are obscured by intestinal gas.

For reference, the book is difficult to use because of the absence of an orderly sequence in its material. Only the briefest sketch of the historical development of the subject is included. A short chapter deals with the technic of filming various parts of the body, but one will search in vain for any mention of the mechanical principles involved in the apparatus. The book's most serious defect, however, is in the quality of reproductions, many of which are so poor as to put a considerable stretch on the imagination of the reader, prompted though he is by the captions.

*Surgical Treatment of the Soft Tissues*. Edited by Frederic W. Bancroft, M.D., and George H. Humphreys, II, M.D., Sc.D. Philadelphia: J. B. Lippincott Company, 1946. \$15.00.

This book, which is an accompanying volume to *The Surgery of the Motor Skeletal System*, discusses injuries and deformities of the soft tissues. Hernia, superficial injuries, thermal injuries, infections, superficial neoplasms and circulatory disturbances are described by recognized authorities in these fields. The book is profusely illustrated, and each chapter has a well chosen up-to-date bibliography. This is a worthy addition to the previous volumes of this set.

## NOTICES

### METROPOLITAN STATE HOSPITAL

The Thirteenth Postgraduate Seminar in Neurology and Psychiatry will begin on Friday, October 10. The program will be as follows: a review course in basic neurology and psychiatry, consisting of eighty-one lectures, to be held every Friday from 2:00 to 10:00 p.m. from October 10 to December 12, 1947, and from January 2 to April 23, 1948, at the Metropolitan State Hospital, 475 Trapelo Road, Waltham, a course in social and special psychiatry, consisting of thirty-six lectures, to be held every Wednesday from 5:30 to 10:00 p.m. from October 15 to December 10, 1947, and from March 17 to May 12, 1948, at the Boston Psychopathic Hospital, 74 Fenwood Road, Boston, and a course in pediatric neuropsychiatry (child psychiatry), consisting of twenty lectures, the first two to be held on Tuesday, October 14 and 28, 1947, from 5:30 to 10:00 p.m. The remaining lectures of the course will be held on alternate Mondays from November 10 to December 8, 1947, and from March 15 to May 10, 1948, at the Walter E. Fernald State School, Waverley.

The seminar is open to all graduate physicians, but the number of vacancies for demonstrations in the review course in basic neurology and psychiatry will be limited to twenty-five in each of the subjects of the course: neuroanatomy, neuropathology and neurophysiology. If the number of applicants exceeds the available teaching facilities, preference will be given to physicians of the Department of Mental

Health and of Veterans Administration hospitals and those preparing for board examinations. Those interested are requested to apply in writing before October 6 to I. William C. Gachler, superintendent, Metropolitan State Hospital, Waltham.

### NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The first regular meeting of the New England Society of Anesthesiologists will be held in the Bigelow Amphitheater of the White Surgical Building, Massachusetts General Hospital, on Tuesday, September 16, at 8 p.m. The program will be as follows:

Operative Morbidity: A dual responsibility. Dr. Mel Saklad, director of anesthesia, Rhode Island Hospital.  
Report of Anesthesia Study Commission of the New England Society of Anesthesiologists.

### NEW YORK ACADEMY OF SCIENCES

The list of speakers at the conference entitled "Antihistamine Agents in Allergy," which will be held at the New York Academy of Sciences on October 3 and 4, is as follows: Sir Henry H. Dale, formerly director of the National Institute for Medical Research, Mount Vernon House, England; Dr. Carl A. Dragstedt, professor of pharmacology, Northwestern University Medical School, Chicago; Dr. M. Rocha e Silva, professor of pharmacology and biochemistry, Instituto Biologica, Sao Paulo, Brazil; Dr. M. W. Chase, Rockefeller Institute, New York City; Dr. E. T. Waters, Banting and Best Department of Medical Research and Department of Physiology, University of Toronto, Toronto; Dr. N. Fell, Camp Detrick, Frederick, Maryland; Dr. D. Bovet, professor of pharmacology, University of Rome; Dr. Rudolf L. Mayer, Division of Research, Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey; Dr. Earl R. Loew, Department of Pharmacology, University of Illinois College of Medicine, Chicago; Dr. Rolf Meier, medical director, Ciba Limited, Basel, Switzerland, and professor of pharmacology and therapeutics, University of Basel; Dr. Charles F. Code, Mayo Foundation, Rochester, Minnesota; and Dr. Samuel M. Feinberg, Department of Allergy, Northwestern University Medical School, Chicago.

Persons desiring to attend the conference may do so by making a request in writing to the executive secretary, Eunice Thomas Miner, Central Park West at Seventy-ninth Street, New York 24, N.Y.

### NEW YORK ACADEMY OF MEDICINE

The Twentieth Graduate Fortnight of the New York Academy of Medicine will be held October 6 through October 17, the subject being "Disorders of Metabolism and the Endocrine Glands." The program includes morning panel discussions, afternoon clinics, evening lectures, scientific exhibits and demonstrations. Complete programs will be mailed to physicians on request.

A physician who is not a fellow of the Academy may obtain registration by sending his name and address, accompanied by a check for five dollars, to the Secretary of the Graduate Fortnight Committee, 2 East 103rd Street, New York 29, New York.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 4

MONDAY, SEPTEMBER 8			
*12:15-1:15 p.m.	Clinicopathological Conference	Peter Bent	Brigham Hospital
TUESDAY, SEPTEMBER 9			
*12:15-1:15 p.m.	Clinicorontgenological Conference	Peter Bent	Brigham Hospital
WEDNESDAY, SEPTEMBER 10			
*12:00 p.m.	Grand Rounds and Clinicopathological Conference (Children's Hospital)	Peter Bent	Brigham Hospital

\*Open to the medical profession

(Notices continued on page xxxi)

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## BACTERIAL ENDOCARDITIS

### Experiences with Penicillin Therapy at the Massachusetts General Hospital, 1944-1946

OGLESBY PAUL, M.D.,\* EDWARD F. BLAND, M.D.,† AND PAUL D. WHITE, M.D.‡

BOSTON

**P**ENICILLIN was first used in the treatment of a case of bacterial endocarditis at the Massachusetts General Hospital in 1944. During the subsequent three-year period 44 patients have received this antibiotic agent with remarkable results, which are to date comparable to those reported from other large clinics. In our series 29 lives that undoubtedly would have been lost only a few years ago have been saved. On the other side of the picture, penicillin treatment is not without its technical difficulties. Attainment of cure is a lengthy and expensive process, often interrupted by unforeseen and at times tragic complications, and an over-all mortality of 20 to 30 per cent still exists. The following review of our recent experience is nevertheless heartening, and we are hopeful that with the passage of another few years the results will be even better.

It has been only recently that unlimited amounts of penicillin have been available, and some of the earlier failures might have been cured today. It should also be pointed out that these patients were treated by various persons both on the general hospital wards and in the private units and that in the beginning no common policy was established regarding dosage, route of administration and duration of treatment. Perhaps this lack of uniformity was of value in giving a broad range of experience, and the present program of therapy has evolved largely as a result of these earlier successes and failures. The methods now employed are outlined below.

## CLINICAL DATA

**Criteria for inclusion.** No case was included unless, in addition to the clinical diagnosis of bacterial endocarditis, a minimum of three blood-

culture flasks were positive for the same organism, or unless the presence of bacterial endocarditis was confirmed at autopsy. Otherwise, no selection of cases was employed, all patients who received penicillin treatment being included, even though such treatment was limited to a few days.

It will be noted that the inclusive term "bacterial endocarditis"—rather than subacute and acute bacterial endocarditis—is employed throughout this paper. Although the vast majority of our cases were typically subacute in type, there were several with a clinical course that might be labeled either subacute or acute. We have therefore preferred to group all our cases under the general heading indicated above.

**Age.** The youngest patient was three and a half and the oldest seventy-two years old. Table 1 presents the number of cases in each age group. It is of interest that the youngest patient and both of those in the eighth decade did well. Age in itself does not seem to be a deterrent to successful treatment.

**Sex.** Twenty-four patients (55 per cent) were males, and 20 (45 per cent) were females.

**Occupation.** Eleven patients belonged to the white-collar group, 10 led moderately active laboring or outdoor lives, 9 were housewives, 5 were students, and in 9 cases there was no definite employment in the period immediately prior to illness.

**Types of heart disease.** Rheumatic heart disease predominated, with emphasis on aortic-valve lesions, as compared with the usual high incidence of mitral-valve lesions in uncomplicated rheumatic cases (Table 2). Thirty-six cases (82 per cent) fell into the rheumatic group, there was combined aortic and mitral disease in 13 patients, apparently pure aortic disease in 6, and valvular disease was considered to be limited to the mitral valve in 17. In addition, 1 patient had calcareous aortic stenosis, 1 had aortic-valve disease, unclassified, and 6 (14 per cent of the total) had congenital heart disease. The last group included 2 patients with the tetralogy of Fallot, 1 with pulmonic stenosis, 1 with subaortic stenosis, 1 with a ventricular septal defect and 1 with a patent ductus arteriosus as well as an

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An example of this was a forty-five-year-old man who was seen by one of us (P. D. W.) in February 1944. The history and physical findings were consistent with the diagnosis of subacute bacterial endocarditis but on blood culture the results were variable and inconclusive (therefore the patient is not included in our series). A brief course of 285,000 units of penicillin, which was all the drug obtainable, produced a brief and dramatic response but the patient died a month later from the effects of cerebral embolism.



aortic-valve lesion (? bicuspid valve, ? rheumatic involvement) A past history of rheumatic fever was obtained in 17 of the 36 rheumatic cases

**Sources of infection** The probable sources of infection are indicated in Table 3 In 19 patients (43 per cent) no convincing data were available The next largest group of cases (30 per cent) fol-

lowed a variety of upper respiratory infections, including the common cold, influenza, grippe, sinusitis and sore throat Dental extractions without prophylactic chemotherapy were implicated as the initiating event in 5 patients (11 per cent) There were 3 patients whose illness had begun with acute gastroenteritis, whether or not such episodes

TABLE 1 Number of Cases and Mortality by Age Groups

AGE GROUP	NO OF CASES	PERCENTAGE OF TOTAL CASES	NO OF DEATHS	MORTALITY %
57				
0-9	1	2	0	0
10-19	7	16	2	29
20-29	12	27	2	17
30-39	7	16	3	43
40-49	0	0	0	0
50-59	9	20	4	44
60-69	6	14	4	67
70-79	2	5	0	0
Totals	44		15	
Average				34

lowed a variety of upper respiratory infections, including the common cold, influenza, grippe, sinusitis and sore throat Dental extractions without prophylactic chemotherapy were implicated as the initiating event in 5 patients (11 per cent) There were 3 patients whose illness had begun with acute gastroenteritis, whether or not such episodes

TABLE 2 Types of Heart Disease

TYPE OF DISEASE	CLINICAL DIAGNOSIS	CLINICAL AND POST-MORTEM DIAGNOSIS	TOTAL CASES	NO	PER-CENTAGE
Rheumatic heart disease				36	82
Mitral valve	16	1			
Mitral and aortic valves	10	3			
Aortic valve	5	1			
Calcific aortic stenosis	1		1	2	
Congenital heart disease			6	14	
Tetralogy of Fallot	1	1			
Pulmonic stenosis	1				
Subaortic stenosis	1				
Ventricular septal defect	1				
Patent ductus arteriosus					
(? bicuspid or rheumatic aortic-valve involvement)	1				
Aortic-valve disease, unclassified		1	1	2	
Totals	37	7	44		

actually served as the portal of entry for the bacteria recovered later from the blood stream may be questioned Single cases followed "virus pneumonia," a criminal abortion, a compound fracture and an apparently normal delivery Of unusual interest is the case of a twenty-seven-year-old tool-maker who, five months before admission, received a compound comminuted fracture of the left thumb The convalescence from this injury was complicated by lymphangitis of the left forearm associated with considerable fever, and he was treated by a physician with sulfadiazine, with disappearance of the

TABLE 3 Antecedent Infections or Other Cause

SOURCE OF INFECTION	NO OF CASES	PERCENTAGE
Unknown	19	43
Upper respiratory infection	13	30
Dental extraction	5	11
Acute gastroenteritis (?)	3	7
Pneumonia	1	2
Normal delivery	1	2
Criminal abortion	1	2
Compound fracture	1	2
Total	44	

hospital He gave a history of rheumatic fever at the age of eleven, and examination revealed the murmurs of aortic regurgitation and mitral stenosis, splenomegaly and clubbing of the fingers Blood cultures grew out alpha-hemolytic streptococci, and

TABLE 4 Symptomatology

SYMPTOMS	NO OF CASES	PERCENTAGE
Feverishness	40	91
Weakness	31	70
Weight loss	27	61
Sweats or chills, or both	26	59
Anorexia	16	36
Rash	12	27
Joint pains	8	18

he responded well to treatment The relation of the fracture to the endocarditis is uncertain

**Symptoms** The outstanding symptom was feverishness, and many patients volunteered the information that the temperatures had frequently been

TABLE 5 Physical Findings at the Time of Admission

PHYSICAL FINDINGS	NO OF CASES	PERCENTAGE
Significant cardiac murmurs	44	100
Splenomegaly	18	41
Pallor	16	36
Petechiae	15	34
Clubbing	10	23
Basal rales	6	14
Hepatomegaly	5	11
Auricular fibrillation	3	7

101 and 102°F or higher Forty cases (91 per cent) were in this group Other symptoms in the order of incidence were weakness, weight loss (16 patients had lost 10 pounds or more), sweats or chills, or both, anorexia, rash or "spots" and joint pains (Table 4) Nine months was the longest period of

recognized illness prior to admission, over 90 per cent of patients having had complaints for six months or less

**Physical findings** Significant murmurs were apparent at the time of admission in 100 per cent of cases, constituting the only physical finding present in all patients in this series. Splenomegaly was next in frequency, being noted in 18 cases (41 per cent). Less common were pallor, petechiae, clubbing, signs of congestive failure and cardiac arrhythmias (Table 5).

The incidence of auricular fibrillation and flutter is of interest, since such arrhythmias are relatively infrequent in bacterial endocarditis. Three patients showed auricular fibrillation on admission, electrocardiographic proof being obtained in each case. In an additional patient auricular flutter was present in the electrocardiogram taken one day after admission, flutter and fibrillation being found on a second tracing two days later. Transient auricular fibrillation, which occurred during the treatment of another case, was also demonstrated by the electrocardiogram. Four additional patients developed gross arrhythmia during hospitalization, and in each case the clinical diagnosis of auricular fibrillation was made but no tracings were obtained. A total of 5 cases (11 per cent) thus had proved auricular fibrillation or flutter, and in 3 of these the arrhythmia had persisted throughout the entire hospital course.

**Major embolic phenomena** Splenic infarction, considered to be present in 7 cases, was manifested by moderate to severe pain in the left upper quadrant coming on abruptly and associated with the appearance of tenderness and often spasm, with or without a palpable spleen. Two of these patients died, and splenic infarction was found at post-mortem examination. One of the latter was associated with infarction and abscess formation ending in a fatal rupture of the spleen (this remarkable finding has been reported elsewhere<sup>1, 2</sup>). In 2 other cases the existence of healed splenic infarction was demonstrated at autopsy, although no clinic evidence had been noted.

**Cerebral phenomena** (presumably embolic) were observed clinically in 7 patients and ranged from episodes of transient confusion, disorientation and aphasia to frank hemiplegias. Three of these patients are now living without evident residual cerebral damage, and 4 have died (1 of a recurrence of endocarditis seventeen months later). An autopsy in 1 of these cases showed a right cerebellar infarct. A diagnosis of cerebral embolism was made in another patient four days before death but was not substantiated by the post-mortem findings.

In 1 patient the appearance of gross hematuria with subsequent left-flank tenderness and spasm was considered clinical evidence of renal infarction. This condition was found at autopsy in another patient although it had not been suspected, and

similarly renal infarction with embolic nephritis and embolic nephritis alone were each discovered once by the pathologist.

Subarachnoid and intracerebral hemorrhage resulting from the rupture of a mycotic aneurysm took place in 2 cases. This occurred on the tenth day of treatment of a thirty-nine-year-old male office worker, who suddenly complained of severe headache and shortly lapsed into coma. Lumbar puncture revealed grossly bloody fluid. Despite the ominous significance of this complication, he survived for another two and a half weeks, finally succumbing to congestive heart failure. At autopsy, in addition to subarachnoid and intracerebral hemorrhage, it was found that rupture of a chorda tendinea of one leaf of the mitral valve had taken place. The other patient had just finished a four weeks' course of therapy, with apparently excellent results, when she suffered a massive subarachnoid and intracerebral hemorrhage and died within a few hours. Post-mortem bacteriologic studies, including careful culture of the involved aortic valve, which had been removed under sterile precautions and ground up, and culture of the heart's blood, were all negative. Samples from twelve blood-culture flasks had also been reported as negative during the period of penicillin treatment. It is believed that the mycotic aneurysm found at autopsy had been sterilized but that death had occurred from the resulting weakness in the arterial wall, with eventual rupture and fatal hemorrhage.<sup>3</sup>

Frank congestive failure, which occurred during the period of hospitalization of 7 patients, was related in at least 1 to the administration of too much physiologic saline solution with the penicillin. A diagnosis of active rheumatic fever was made in 2 cases.

**Blood studies** A hemoglobin level of less than 12 gm per 100 cc or a red-cell count of less than 4,000,000 was present in 68 per cent of cases, and the initial white-cell count was over 10,000 in 55 per cent. The admission blood smear showed 80 per cent or more neutrophils in 36 per cent of patients.

#### BACTERIOLOGIC DATA

**Bacteriology** Table 6 lists the organisms isolated in the 44 cases. It will be noted that no organism was obtained in 1 case—that of a gravely ill fifty-one-year-old man who died after four and a half days of penicillin treatment and in whom the diagnosis was confirmed by post-mortem examination, typical vegetations being present on the aortic valve. The case was medicolegal, and no post-mortem bacteriologic studies were done.

As would be anticipated, the alpha-hemolytic streptococcus was the organism most frequently found, accounting for 82 per cent of the series. Mixed alpha-hemolytic and beta-hemolytic streptococcal infections occurred in 2 cases, beta-hemolytic

and gamma-type streptococci were each responsible in 1, and *Staphylococcus albus* in 2. It is of interest that both cases with staphylococcal infection responded satisfactorily to treatment.

**Sensitivity determinations** In 31 cases data on the bacterial sensitivity to penicillin are available. These figures are presented in Table 7 (in cases in which more than one determination was made and a change in sensitivity reported, we have recorded

TABLE 6 *Organisms Obtained by Blood Culture*

ORGANISM	NO OF CASES	PERCENTAGE
Alpha-hemolytic streptococcus	36	82
Alpha-hemolytic and beta-hemolytic streptococci	2	5
Nonhemolytic (? alpha-hemolytic) streptococcus	1	2
Beta-hemolytic streptococcus	1	2
Nonhemolytic (gamma type) streptococcus	1	2
<i>Staph. albus</i>	2	5
None	1	2

the greatest rather than the least resistance to penicillin in vitro). Fortunately, the bulk of the strains isolated were inhibited in the test tube by reasonable levels of the drug, but five of them grew in a medium containing 1 or more units per cubic centimeter. The most resistant case required 8 units of penicillin per cubic centimeter of broth to inhibit growth.

Definite increases in the resistance of the organisms to penicillin were noted in 2 cases. In 1, a tenfold rise was reported, and in the other, the resistance increased one hundred and thirty times.

The significance of such information and its value in guiding treatment are not entirely clear. On the

daily, was infected with a strain of the alpha-hemolytic streptococcus for which a level of 6 units was necessary. In no case in which the sensitivity was high did failure result clearly from inability to sterilize the blood stream. On the other hand, one strain of the alpha-hemolytic streptococcus that was reported to require 25 units of penicillin per cubic centimeter of broth to inhibit growth was successfully treated with relatively small doses (192,000 units daily for nineteen days). The patient died while visiting in another city six months after discharge, having had no symptoms suggesting a return of infection and with repeatedly negative blood cultures throughout that period. The cause of death is not definitely known, although it was stated that the patient died from heart failure. It is possible that the sensitivity report was in error. In another case blood levels four to eighteen times those indicated in the test tube as being effective were maintained without evidence of sterilization of the blood stream.

It is clear that such bacteriologic procedures must be carefully performed if technical sources of error are to be eliminated and if accuracy is to be obtained. In these studies it is unfortunate that more individual technical attention was not available. The duration of chemotherapy, the manner of administration of the drug and the patient's own immune response, not to mention the anatomic features of the valvular lesion itself, must be considered before one relies too heavily on evidence in vitro, valuable though that evidence may be.

### THERAPY

**Routes of administration** Considerable variation in the manner of administration of penicillin is found on analysis of these 44 cases. The methods employed included intermittent intramuscular injections at intervals of one, two, three and four hours, intramuscular injections of penicillin in oil and wax three times daily, constant intramuscular and intravenous drips and oral ingestion of the drug. No final conclusions regarding the efficacy of any one method can be drawn from the data at hand without a careful correlation with the dosage, resistance of the organism and blood levels obtained. Unfortunately, the information available does not lend itself to such an analysis. Isolated observations are of interest, however—for example, the facts that 1 case was satisfactorily treated solely by the oral route (in amounts of 100,000 units of penicillin every two hours) and that another patient did well after a course of only 33,000 units every four hours intramuscularly for three weeks. The results of penicillin in peanut-oil and beeswax have been reported elsewhere,<sup>1,2</sup> but it was notable that at autopsy after a month of such administration there were large gluteal abscesses at the sites of injection, with extensive muscle necrosis. Cultures obtained from the abscesses revealed the same

TABLE 7 *Bacterial Sensitivity to Penicillin in Vitro*

PENICILLIN REQUIRED TO INHIBIT GROWTH units/cubic centimeter	NO OF CASES
Less than 0.1	19
0.1 to 0.4	5
0.5 to 0.9	2
1.0 to 4.9	2
5.0 to 10.0	3
Total	31

whole, determinations of bacterial sensitivity have been found a reliable and useful method of detecting patients in whom unusually large doses of penicillin will be required if cure is to be obtained. The correlation with clinical observations is fairly satisfactory. For example, the 2 patients who remained extremely ill and whose blood cultures continued persistently positive despite doses of 8,000,000 and 15,000,000 units a day, respectively, harbored organisms with a high resistance in vitro, requiring respectively 6 and 8 units of penicillin per cubic centimeter of broth to inhibit growth. Another patient, who was finally cured by 10,000,000 units

organism that had been isolated from the patient's blood stream (the alpha-hemolytic streptococcus)

When massive doses of penicillin are not employed, the constant intramuscular drip (in the anterior thigh muscles) has been well tolerated, and the patients themselves have found it to be more comfortable than the other parenteral methods. If a satisfactory aseptic technic is employed at the time of changing the needles and if the site of injection is changed every three or four days, the risk of local abscess formation is minimal. In 5 cases so treated no difficulty was encountered (Four of these were thus treated over a period of one month, and 1 for two weeks.) In 2 additional patients who received massive doses of the drug mild local infection, which occurred after three and six weeks of constant intramuscular administration, was clearly due in 1 to gross abuse of the dressing on the part of the patient, who regularly pulled out the needle unless restrained, and in the other possibly to faulty technic. This route becomes painful if too large a volume of solution is used (we limit the amount to 800 to 1000 cc daily), if the concentration of penicillin is high (unless 0.1 per cent procaine hydrochloride is added) or if little muscle tissue is available. In certain cases other routes, such as constant intravenous and two-hourly intermittent intramuscular injections, are advisable.

It has been our experience that satisfactory blood levels are maintained with the constant intramuscular method. We have not, however, routinely determined the penicillin blood levels in the same patient, comparing constant intramuscular and constant intravenous drips. Loewe<sup>4</sup> has found the latter method to give higher blood levels than the former. We are at present investigating this aspect of the problem. We have also found that the use of physiologic saline solution as the vehicle for dissolving the drug is at times hazardous when the cardiac reserve is limited, and we prefer in such cases to employ 5 per cent glucose in distilled water.

**Dosage and duration.** The smallest amount of penicillin that resulted in cure was 2,685,000 units, given in a short course (fifteen days), mainly by intravenous drip. The largest amount employed was 442,000,000 units, given over three hundred and fourteen days by varying routes (finally by hourly intramuscular injections totaling 10,000,000 units daily for seven days, followed by forty-two days of 5,000,000 units daily by intravenous drip). In retrospect, had large supplies of the drug been available, it would have been cheaper and more satisfactory to have resorted to massive doses much earlier in this patient. Between these extremes fall the bulk of the recovered patients, who, on the average, were successfully treated with a three-week course of 500,000 units a day.

Since the individual patient is not necessarily an "average case," careful bacteriologic control is con-

sidered essential to ascertaining the optimal dose of the drug. An amount of penicillin that will maintain a blood level at least five times that indicated *in vitro* is regarded as being necessary to inhibit growth of the organism. Should positive blood cultures appear despite achievement of this goal, larger doses should be employed. Once a satisfactory daily dose has been established, we now recommend a full four weeks' course, the therapy being halted arbitrarily at the end of that time to evaluate the situation. We have not infrequently observed a low-grade fever to persist throughout the entire course of penicillin therapy, regardless of the method of administration, only to disappear completely once treatment has been stopped. The presence of mild fever is not in itself a guide to success or failure under these conditions.

**Other methods.** When difficulty was encountered in controlling the infection with penicillin alone, additional measures were employed. Sulfadiazine was given to 12 patients for varying periods, and sulfathiazole and sulfamerazine each were tried once. In 9 patients benzoic acid was administered in an effort to elevate the penicillin blood level, and 1 patient received ten typhoid-vaccine chills. There was no clear evidence that any of these measures were of significance in the final results.

A ten-day course of streptomycin (in doses of 4 gm daily) was without effect in a sixty-one-year-old man infected with alpha-hemolytic streptococci, even though the organism was moderately sensitive *in vitro*. We have also recently treated a thirty-two-year-old housewife (who is not included in this series) whose blood cultures grew out *Haemophilus parainfluenzae* with great difficulty.<sup>5</sup> She had been ill for sixteen months, although with minimal symptoms when treatment was instituted, had rheumatic heart disease with aortic and mitral involvement and had been unsuccessfully treated with penicillin elsewhere and by us. She developed a severe papular dermatitis accompanied by a high temperature at the end of the first week of streptomycin therapy but responded satisfactorily to Benadryl and Pyribenzamine. Treatment was continued over the course of seventeen days notwithstanding this complication and the subsequent appearance of labyrinthitis, and although the follow-up period is as yet brief, cure seems to have been achieved.

Transfusions were given to 15 patients. Ligation of a patent ductus arteriosus was performed in 1 case, supported by penicillin therapy, and the patient is well ten months later. Anticoagulants were not employed, owing to our belief that satisfactory results can be achieved without them and that an appreciable hazard accompanies their use. We have had several patients (as noted previously) who have survived cerebrovascular accidents occurring during treatment, we suspect that these pa-

tients might not now be alive if the clotting time had been prolonged at the time of these episodes

### RESULTS

The results are indicated in Table 8. It will be seen that 29 patients are now alive, making a survival rate of 66 per cent.

Of the 15 fatal cases, 2 can clearly be classed as complete therapeutic failures (one critically ill patient failed to respond both to 15,000,000 units of penicillin and 4 gm of streptomycin a day, and in the other case therapy was given up after

TABLE 8 *Results of Penicillin Treatment in 44 Cases*

RESULT	NO OF CASES	PER-CENTAGE
Patient living without evidence of infection	29	66
Death from recurrence seventeen months after discharge	1	2
Death with infection apparently eliminated	6	14
From pulmonary embolism ten days after penicillin was stopped	1	
From subarachnoid hemorrhage due to ruptured sterile mycotic aneurysm five days after penicillin therapy was stopped	1	
From congestive failure one, four and seven and a half months, respectively after discharge	3	
From underlying heart disease six months after discharge	1	
Death with infection probably eliminated	2	5
From cerebral embolism during treatment with all blood cultures negative after penicillin treatment began	1	
From congestive failure, pulmonary infarcts and pneumonia during treatment with all blood cultures negative after penicillin treatment began	1	
Death with infection not eliminated	6	14
From congestive failure after only two and four and a half days of penicillin therapy, respectively	2	
From ruptured spleen after twenty five days of penicillin therapy	1	
From ruptured mycotic aneurysm and congestive failure after twenty-nine days of penicillin therapy	1	
After massive doses of penicillin had completely failed to control the infection	2	

8,000,000 units daily had been ineffective at a time when penicillin was still scarce)

Six other patients succumbed during the course of treatment. In 2 of these chemotherapy had just been started, whereas the remaining 4 died from complications of their disease before the administration of penicillin had been stopped. Two additional patients died from pulmonary embolism (clinical diagnosis) and a subarachnoid hemorrhage, respectively, after the cessation of penicillin. In both cases all blood cultures after the institution of chemotherapy had been negative, and, in addition, at post-mortem examination in 1 the heart blood and ground-up aortic valve were normal on culture.

Five other patients died after discharge from the hospital. Four of these died of cardiac conditions (3 from congestive failure, and 1 of causes not clearly ascertained) without clinical or laboratory evidence of bacterial endocarditis. All had been followed with repeatedly negative blood . . . Another patient died at another hospital sev-

months after discharge, of a recurrence of the disease, having been entirely free of evidence of active infection during the intervening period.

**Follow-up data** We have been able to obtain information regarding the recent status of all 29 living patients. One of these cases although a penicillin cure, should probably not be credited to us, since blood cultures taken in a distant city two months after discharge from our care were again positive for streptococci. The patient was retreated twice by a physician with large doses of penicillin, and a recent report states that he is in excellent health and is attending college. It is assumed that the original infection had never been cured, despite negative blood cultures in the immediate convalescent period. Of the remaining 28 survivors, 3 have been followed for less than six months, 7 for six months to one year, 8 for twelve to eighteen months, 4 for eighteen to twenty-four months, and 6 for two years or more. The lives of 6 of these patients are definitely restricted by cardiac disability.

### SUMMARY

Forty-four patients with bacterial endocarditis received penicillin at the Massachusetts General Hospital in the three-year period 1944-1946. Twenty-nine (66 per cent) are living and are considered cured.

One patient died from a second attack of bacterial endocarditis, and 8 others succumbed to cardiovascular complications of the disease, although the infection itself appeared to have been overcome. Six patients died without evidence of control of the bacteremia.

Rheumatic heart disease was present in 82 per cent of cases in the series, 14 per cent were diagnosed as having congenital heart disease, 1 case (2 per cent) was classified as having calcareous aortic stenosis, and in another case (2 per cent) the nature of the underlying cardiac lesion was unknown.

Upper respiratory infections preceded the endocarditis in 30 per cent of cases, and extractions of teeth in 11 per cent.

Alpha-hemolytic streptococci were responsible for 82 per cent of the infections.

There were 5 cases of marked bacterial resistance to penicillin in vitro, 2 of these patients were cured.

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## DIAGNOSIS AND MANAGEMENT OF RENAL-ARTERY THROMBOSIS\*

## Report of a Case

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**T**HROMBOSIS of the renal artery is not a frequent condition, but it is not nearly so rare as is indicated by the number of times it is diagnosed. Practically all the cases reported are those found at autopsy or operation, but it is often possible to make an accurate diagnosis with present methods and with the condition in mind as a possibility.

Renal-artery thrombosis is not synonymous with renal infarction, for the latter is probably much more frequently caused by venous thrombosis, which is due to various inflammatory and traumatic lesions affecting the renal veins. Also, multiple small renal infarctions are a common autopsy finding when they were of little clinical significance in the patient's life. This paper does not propose to consider these venous or small arteriolar occlusions; it is concerned with thrombosis of the renal artery or its major branches.

This condition, when seen clinically, is usually confused with acute surgical diseases of the urinary tract or of the intra-abdominal organs, or with a medical emergency arising from acute disease of cardiorespiratory origin. The patient may be subjected to needless operation, or much time may be lost, with attention centered elsewhere from the true site of the disease.

The purpose of this paper is to present a case of definite ante-mortem diagnosis, with a review of the salient features that should be of value to others in the recognition of the condition. It is maintained that renal-artery thrombosis is one manifestation of general atheromatous vascular disease and may be diagnosed by history, physical examination, laboratory findings and urologic examination. Probably the most important single factor in diagnosis is its inclusion in the mind of the examiner as a clinical possibility.

## DIAGNOSIS

The presenting symptom of renal-artery occlusion is pain. Unfortunately, this pain is not a characteristic or typical one—the only consistent feature is that it is rather severe. The onset is usually sudden, but one may be misled by a more gradual onset in which the maximum intensity is reached only after several hours.

In most cases the site of the pain is the general region of the disease, which means the flank or the hypochondrium. Either dorsal or ventral pain may predominate, and in such cases the examiner may suspect disorders of the urinary or digestive tract. The pain may go through and through, or may radiate to the lower quadrant or to the chest. It is rather constant—not colicky—and is described as both sharp and dull.

When the radiation is to the chest, the pain may simulate that of coronary thrombosis. Two such reports have been presented by Wolffe<sup>1</sup> and White.<sup>2</sup> Also, with pain in this region, pneumonia and pleuritis must be excluded.

Urinary symptoms are said to be present in only a small percentage of cases. The condition does not strongly suggest ureteral colic, but, of course, the two diseases cannot definitely be distinguished by history. Hematuria and hemoglobinuria, if present, more probably come from partial infarction or infarction due to venous occlusion, in which there is marked renal congestion, as opposed to renal-artery occlusion, in which there is a complete anemia.

Gastrointestinal symptoms are frequent and consist of nausea and vomiting. These, along with upper abdominal pain, may easily direct attention to the digestive tract exclusively.

A careful past history is of utmost importance, with particular emphasis on the cardiovascular, digestive and urinary systems.

The general appearance of the patient is that of acute illness. The temperature is usually slightly elevated, and may be as high as 102°F. The blood pressure and pulse are usually not directly affected by the condition, but are significant in the evaluation of the general cardiovascular status. Vascular disease is the primary cause of the condition, and a major clue may be detected by the taking of the patient's pulse.

The physical findings at the site of the pain are variable. There is usually tenderness, but marked tenderness may be accompanied by absolutely no rigidity. Muscle spasm, when present, is of the voluntary type—not that of peritoneal irritation. Abdominal distention is common. Peristalsis is usually normal, but the pain is rarely sufficient to silence it with a paralytic ileus. Pelvic and rectal examination are noncontributory.

Careful attention must be given to the cardiovascular system. In addition to the history and

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physical examination, an electrocardiogram should be obtained. Arteriosclerosis, hypertension and cardiac disorders as manifested by enlargement, murmurs and arrhythmias are the veritable basis for a renal vascular accident. Indeed, renal-artery thrombosis is only a part of generalized atheroma-

The most important single factor in the diagnosis is a urologic examination, by cystoscopy and ureteral catheterization and pyelography. In cases of complete occlusion of the renal artery, there is absence of urine on the side involved, with a failure of the kidney to excrete dye such as phenolsulfonephthalein or indigocarmine. This is further confirmed by failure to excrete Diodrast in an excretory urogram. Retrograde pyelography early in the disease shows an anatomically normal kidney. This is the actual finding on which the diagnosis is based—an anatomically normal kidney that has no function. Wolffe<sup>1</sup> states that in cases of occlusion of a major branch of the renal artery affecting approximately



FIGURE 1 *Right Retrograde Pyelogram Taken on the Day of Admission*

*The kidney appears to be normal anatomically*

tous vascular disease, and this fact cannot be too strongly emphasized. In the case presented below, the patient had had a previous cerebral thrombosis and finally died of myocardial infarction, showing the generalized involvement of the arterial system. The renal-artery thrombosis may strike first, however, and with abdominal pain and digestive symptoms predominating, it may be more difficult to make a prompt and accurate diagnosis.

Leukocytosis is usually present. The urine may be normal, but is likelier to have albumin, a low specific gravity and the changes found in cardiovascular renal disease. Hematuria is occasionally observed, as mentioned above. There may be elevation of the nonprotein nitrogen if the other kidney is diseased and cannot assume the entire excretory function.



FIGURE 2 *Retrograde Pyelogram Taken One Week after Admission*

*There is diminution in the size of the right kidney*

half the kidney the diagnosis is best shown by excretory urograms. The infarcted portion of the kidney is poorly demonstrated by the fact of no concentration of the dye in the tubules of that portion, and the pyelogram is hazy and indistinct in that pole. Our opinion is that this finding is more conclusive late in the condition rather than early, for at first the configuration of the renal pelvis is not changed anatomically. Serial pyelography demonstrates a progressive atrophy of the

kidney involved, and may show compensatory hypertrophy of the other kidney. In the x-ray film of the abdomen, attention should be paid to calcification of the great abdominal vessels — a good indication that such changes may exist also in the renal vessels.

Nelson<sup>2</sup> and others have described a highly accurate diagnostic procedure in the aortogram, but this is too formidable to be of general use. Catheterization of the vena cava and renal vein is now performed in many cases for physiologic and pathological studies, and may be of value. Such a procedure was used in the case reported below.



FIGURE 3 Retrograde Pyelogram Taken Three Weeks after Admission.

This shows still further diminution in size of the right kidney. The configuration remains normal.

and aided immeasurably in the diagnosis by obtaining no blood flow from the kidney involved.

#### MANAGEMENT

The management of the condition is medical, and the prime requisite is rest. Nothing is to be gained by surgical intervention, and of course the patient is a poor anesthetic risk on account of the possibility of other occlusions. Fluid balance, cardiac failure, function of the remaining kidney and all other general features of the condition deserve the major

consideration, for nothing is to be done for the thrombosis that has already occurred. Total occlusion leaves a functionless kidney, but occlusion of only a major arterial branch may leave enough

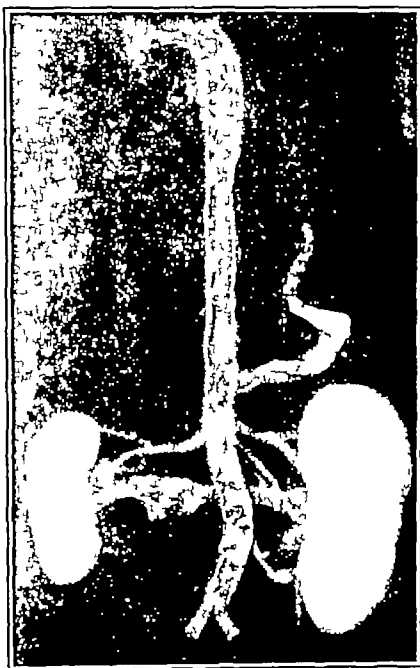


FIGURE 4 Post-Mortem Roentgenogram of the Kidneys, Renal Vessels and Aorta.

Note the arterial calcification and the comparative size of the kidneys.

renal function to be of value to the life of a patient whose circulatory apparatus has suffered such severe changes as to allow thrombosis to occur.

#### CASE REPORT

L. M. G. (A-65313) a 62-year-old woman was admitted to the hospital on April 9, 1946. She complained of pain in the right upper quadrant of the abdomen of 2 days duration. The pain was constant and severe, not colicky in nature and radiated through to the right flank. Nausea and vomiting began shortly after the onset of the pain and persisted until admission. The patient had had no bowel movement for 2 days. The urinary symptoms of hematuria, dysuria and frequency were denied.

The significant past history was confined to the cardiovascular system. The patient was known to have had hypertension for several years. One year previously she had suffered a mild cerebral accident, with aphasia, facial weakness. These symptoms were made a complete recovery. She had worked until the onset of the



Physical examination revealed an elderly woman apparently ill and in acute distress. Significant physical findings were confined to the abdomen and the circulatory system. The abdomen was moderately distended. There was marked tenderness in the right upper quadrant, but no muscle spasm. There was even more marked tenderness in the right costo-vertebral angle, with moderate voluntary muscle spasm. No mass could be felt. Peristalsis was present. Rebound tenderness could not be detected. The heart was enlarged to the left, without shocks, thrills or murmurs. The rate was 76, showing approximately 14 beats per minute dropped, in comparison of the apical and radial rates. The rhythm was irregular, owing to frequent premature ventricular contractions, and the irregularity seemed even more striking at the radial pulse. The peripheral vessels were sclerotic, and the eyegrounds showed marked arteriolar constriction.

The temperature was 100°F, the respirations 18, and the blood pressure 160/80.

A specimen of bladder urine obtained through a catheter was normal except for a faintly positive test for albumin. Examination of the blood disclosed a red-cell count of 4,600,000, with a hemoglobin of 14 gm per 100 cc., and a white-cell count of 18,200, with 88 per cent neutrophils and 12 per cent lymphocytes. The nonprotein nitrogen was 46 mg per 100 cc.

On the basis of these findings the patient was admitted to the Surgical Service for possible gall-bladder disease, appendicitis or partial intestinal obstruction. On the night of admission a urologic examination was performed. Cystoscopy revealed a normal bladder, but no urine was seen to spurt from the right ureteral orifice. Both ureters were catheterized easily, and the urine from the left side was normal. No urine was obtained from the right kidney, although the catheter was proved to be patent and in the kidney pelvis. The right kidney failed to excrete indigocarmine in 20 minutes, whereas the excretion on the left was prompt and adequate. An excretory urogram showed good excretion on the left, but none on the right. Retrograde pyelography demonstrated that both kidneys were normal anatomically. It was noted in all the roentgenograms that there was calcification of the great abdominal vessels.

A diagnosis of complete occlusion of the right renal artery was made, and the patient was transferred to the Urological Service. The electrocardiographic diagnosis was isolated ventricular premature systoles.

For the next 4 weeks the patient continued to be quite ill. She complained of pain, but it steadily became less. She was semistuporous and lethargic. The blood pressure fluctuated from 160/80 on admission to 250/140, averaging 220/120. The nonprotein nitrogen rose to 68 mg per 100 cc 1 week after admission, and then made a gradual decrease to 32 mg per 100 cc. within 4 weeks.

Five days after admission the patient experienced an episode of gross hematuria, with nausea and vomiting, the skin was cold and clammy, and the blood pressure was at its height. She was nearly comatose, and the prognosis was grave. The hematuria ceased within 24 hours, and no urologic studies were made during that time, so that the source of the bleeding was undetermined. Thereafter, the urine remained clear, but continued to show a positive test for albumin and a low specific gravity.

At weekly intervals during the hospital stay retrograde pyelograms were made, and progressive atrophy of the right kidney was observed. No resumption of renal function on that side was noted. The left kidney remained normal. These serial studies were performed on the same table and with the same technic, so that exact measurement of the atrophy was possible (Fig 1, 2 and 3). The diminution in size was evident at a glance, and measurement revealed a change of 2 cm in length and 7 mm in width within 3 weeks.

Two weeks after admission, catheterization of the right renal vein was performed as a diagnostic procedure. This was done with a No 8 Fr catheter, introduced in a vein in the antecubital fossa and passed up into the subclavian vein, down the superior vena cava and into the inferior vena cava. Under fluoroscopic vision the right renal vein was catheterized, no flow of blood being obtained from this vessel.

Within a month the patient was considerably improved. She was sitting up and eating and was much clearer mentally. Six weeks after admission she was allowed to go home, to be followed weekly in the outpatient clinic.

She did not return to the clinic as directed. Three weeks after discharge she was readmitted through the Emergency Clinic. She was comatose, with a blood pressure of 156/100, a nonprotein nitrogen of 68 mg per 100 cc., and an irregular pulse as previously. She was apparently in extremis and became progressively weaker. She died 48 hours after the second admission.

**Autopsy.** Post-mortem examination confirmed the diagnosis of complete thrombosis of the right renal artery with bilateral arterioneurophrosclerosis (Fig 4). There was generalized arteriosclerosis, and the primary cause of death was a myocardial infarction due to thrombosis of the left coronary artery. The splenic artery and abdominal aorta showed the severe calcification as detected by x-ray study.

## SUMMARY

The pathogenesis, diagnosis and management of renal-artery thrombosis are discussed.

Renal-artery thrombosis is considered to be one manifestation of generalized atheromatous disease of the arterial system. The condition is more frequent than is generally recognized and can be diagnosed with present methods.

A case of complete occlusion of the right renal artery due to thrombosis in which the ante-mortem diagnosis was confirmed by autopsy is presented.

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## MILKMAN'S SYNDROME\*

## Report of a Case

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FROM time to time in routine radiologic bone studies lesions are encountered whose etiology is difficult to determine. Such a case is reported below because of its interest from a radiologic and medical point of view. Milkman<sup>1</sup> presented a case of multiple spontaneous idiopathic symmetrical fractures in which forty-three fractures were noted and for which no etiology was established. Since Milkman's report 19 additional cases have been reported in the literature, with a review by Edeikin and Schneberg.<sup>2</sup> Of these cases, 16 were reported from Europe. All except 1 occurred in women.

The main clinical characteristics of Milkman's syndrome are the predilection for middle-aged women, intermittent backache, pains in the legs, fatigue, waddling gait, difficulty in changing positions, good nutritional and constitutional condition despite widespread bone changes and, in the later stages, bedfastness. Radiographically, the disease is characterized primarily by generalized osteoporosis and by a multiplicity of symmetrical fractures with inadequate healing. The disease in the early phase is characterized by focal osteoporotic areas, which progress to linear areas of rarefaction known as Looser's zones and generally called "pseudofractures." Above and below the lesions the bone appears normal except for osteoporosis. As the disease progresses, these lesions may give rise to displacement at the site of the fracture, resulting in such deformities as coxa vara, but predominantly there are few cases of displacement and the lesions appear to remain static radiographically, with no evidence of healing.

From a laboratory point of view, nothing pathognomonic has been found. In the case presented below, extensive laboratory studies were conspicuous only by the normality of the findings.

The diseases in which Looser's zones or pseudofractures have been described and thus must be considered in a differential diagnosis are osteomalacia, rickets and late rickets, renal rickets, celiac disease, chronic idiopathic steatorrhea, Gee's disease (intestinal infantilism), nontropical sprue, sprue, osteogenesis imperfecta (early and late), fragilitas osium, hyperparathyroidism, hyperthyroidism, osteitis deformans (Paget's disease), bone dystrophy secondary to adrenopituitary dysfunction, severe chronic acidosis (hyperglycemia), congenital syphilis, osteomyelitis, osteopetrosis ("marble bones"), march fractures and blood dyscrasias.

Despite extensive study in the cases reported as Milkman's syndrome, no etiologic factor has been revealed, and there is nothing specific from a histologic study of the involved bone.

In the treatment of this condition, as in any disease in which the etiologic agent is unknown, a great many therapeutic agents have been tried without any beneficial results. Primarily, calcium and vitamin A and D therapy have been used most extensively. Other agents that have been used are arsenicals, ultraviolet rays, bone grafts and multivitamins.

Hopf<sup>4</sup> stated that calcium and vitamin D gave immediate and lasting relief. Debray,<sup>5</sup> using phosphorus (phospho-calcique) and arsenicals reported a "functional cure." Edeikin<sup>2</sup> claimed a remission with vitamin D and ultraviolet-ray therapy. In view of the inability to demonstrate an etiologic agent, the failure of similar therapy in other cases, as well as in the case reported below, and the intermittent clinical character of the condition, it is doubtful that such therapy is of lasting aid in bona fide cases. Thus, another clinical characteristic of this syndrome is its failure to respond to known therapeutic agents.

A 37-year-old man had felt perfectly well until March 1943. He had had 21 years of service in the Army and until the onset of the present illness had served satisfactorily. At that time while returning from a 27 mile road march he slipped and fell injuring the right hip. He was able to continue the march although the hip hurt. The pain continued with some radiation down the right thigh to the knee. For the next 2 months he had intermittent severe pain in the hip as well as in the lower part of the back and was seen on sick call at various intervals. In June the first x-ray films of the hip were taken and revealed some thinning of the osseous articular cortex and a minor degree of generalized osteoporosis of the head of the right femur and the adjacent acetabulum. Some shortening of the neck of the right femur, with anterior angulation of the head on the neck was also noted. A diagnosis of traumatic arthritis of the right hip was made and the orthopedic consultant noted a 2-cm. shortening of the right lower extremity. The patient was sure that the limp had begun after the injury in March and denied previous injury or a possible old fracture and the Army records confirmed these facts. The patient was returned to duty and the pain in the right hip, low back and legs continued.

In August the patient went through mustard gas in a gas chamber and burns of both legs below the knee and on the right forearm developed. The resultant rash was first red and healed slowly being replaced by a brownish pigmentation that remained particularly on the right leg. In the same month he was again hospitalized. X-ray films were obtained and he was returned to duty with a diagnosis of arthritis of the right hip. The x-ray films of the lumbar spine, pelvis, chest and hip again revealed only the lesion in the right hip; the report stated that the femoral head had the appearance of an old slipped epiphysis that had fused in malposition without undue destruction. It was noted at that time that the patient had a distinct waddling gait. The observation was made that, despite the fact that the general clinical impression and x-ray examination suggested long

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standing illness, the symptoms were of relatively recent origin. In November the patient was transferred to an armored division and because of the continued pain and limp was unable to perform duty satisfactorily. By February there seemed to be some alleviation of the pain, but at that time a rash developed on both legs below the knees and on the right forearm. This was over the skin area that had been subjected to the mustard burn some months previously. The patient was transferred from several units

Physical examination revealed a patient who was 5 feet, 7½ inches tall. The skin was clear except for brown areas of pigmentation over both legs extending from 10 cm. below the knees to just above the ankles. There was a large brown pigmented area on the lateral side of the left foot. The eyes, ears, nose and throat were normal. There were no palpable lymph nodes. The heart and lungs were normal. The abdomen revealed no tenderness, palpable viscera or masses. The genitourinary system was normal. Rectal examination was negative. The patient walked with a marked limp and a waddling gait. He had difficulty in movement requiring flexion of the low back or right hip. The right leg was approximately 4 cm. shorter than the left. Motion was free in all normal excursions in the left hip. There was slight tenderness over the right sacroiliac region and in the right hip joint. There was no noticeable scoliosis of the spine. There was moderate generalized weakness but no gross



FIGURE 1 *Pseudofractures of the Spinous Processes of the Fifth, Sixth and Seventh Cervical Segments, with Generalized Osteoporosis and Biconcave Lower Cervical Bodies*

because of inability to perform duty satisfactorily. The pain and stiffness prevented him from getting out of a chair rapidly or from walking fast, and he stumbled and fell rather frequently. Because of the continuing difficulty, he was again admitted to an Army hospital on March 16, 1945.

In the interval there had been an increase in the difficulty in walking, in the limp with waddling gait, in the pain in the low back and the right hip and occasionally in the right leg. These symptoms had remained practically unchanged to date. The patient's general health had otherwise been good, and he had gained about 10 pounds in weight since the onset of the illness.

The patient had served in Panama from 1924 to 1930, in Hawaii from 1930 to 1933 and from 1938 to 1940. The patient drank occasionally and smoked about 1½ packages of cigarettes daily. He used no habit-forming drugs.

The patient's mother was living and well at 68 years of age, and his father, 70 years of age, was in good health. The patient had two siblings, both living and well. There was no family history of diabetes, tuberculosis, syphilis or cancer. No member of the family, to his knowledge, had had arthritis, bone disease or nervous or mental disorders.

The patient had had the usual childhood diseases but no scarlet fever, diphtheria or rheumatic fever. He had had malaria in 1926 while in Panama, but there had been no recurrence. In 1942, after an inoculation for yellow fever, he had a mild case of jaundice with no sequelae. There had been no injuries of significance.

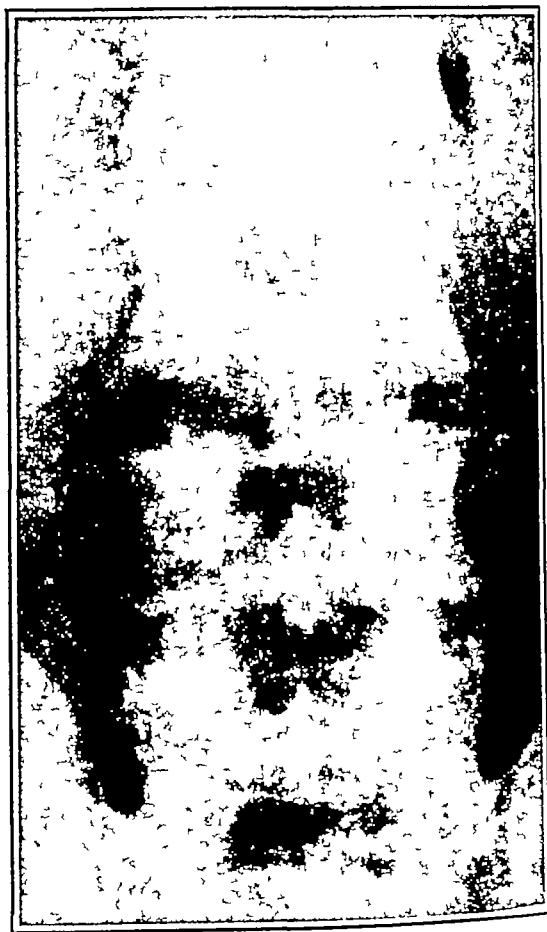


FIGURE 2 *Bilateral Interarticular Isthmus Hiatus of the Third, Fourth and Fifth Lumbar Segments*

atrophy of the muscular system. Neurologic examination was negative, and the reflexes were physiologic.

The blood pressure was 120/80.

X-ray studies in March, 1945, disclosed a moderate degree of generalized osteoporosis. An irregular longitudinal line of rarefaction extending across the superior margin of the left acetabulum was noted. There was no evidence of cartilage destruction in the joints. Little or no bone production was noted in any of the localized areas of bone destruction. There was no bowing of the femurs. The bone changes were noted to be predominantly within the cortex. Later x-ray films revealed narrowing of the bodies of the fifth and sixth dorsal vertebrae and pseudofractures of the spinous processes of the fifth, sixth and seventh cervical vertebrae (Fig. 1). Further x-ray changes included generalized osteoporosis and pseudofractures of the interarticular isthmus hiatus bilat

erally in the third, fourth and fifth lumbar segments (Fig 2) of the second to the fourth and the sixth seventh ninth tenth and eleventh left ribs and the second, seventh, eighth and tenth right ribs, of the manubrium of the acromioclavicular processes and the middle thirds of both scapular bodies below the spines (Fig 3), of both radial necks (Fig 4), of

examination showed a red-cell count of 5,500,000, with 16.09 gm of hemoglobin, and a white-cell count of 5600, with 52 per cent neutrophils, 47 per cent lymphocytes and 1 per cent monocytes. The clotting time was 3 minutes, and the bleeding time 2 minutes. The hematocrit was 47 vol. per cent, with a sedimentation rate of 7 mm in 1 hour

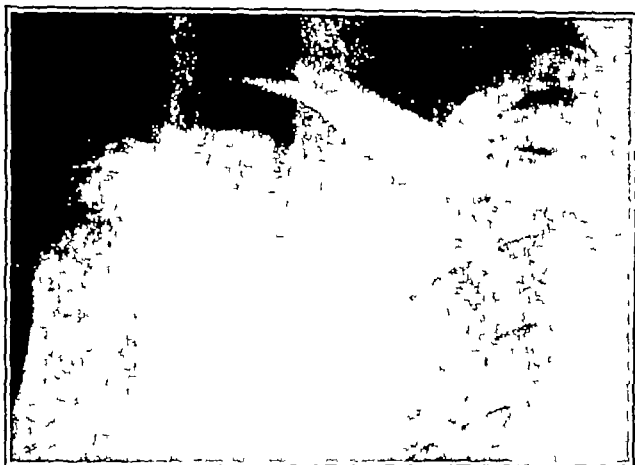


FIGURE 3 *Pseudo-fractures of the Acromion, a Linear Fracture of the Body of the Scapula and Fractures of the Second Third and Fourth Ribs*

the distal phalanx of the left middle finger (Fig 5), of the superior margin of the left acetabulum (Fig 6), of the neck of the right femur with a coxa vara deformity (Fig 7) and of both patellas (linear). An intravenous pyelogram

Blood Kahn and Wassermann tests were repeatedly negative. Examination of the spinal fluid was within normal limits. Repeated urinalyses showed only one significant finding — a ++ Benedict's test for glucose on several examinations.

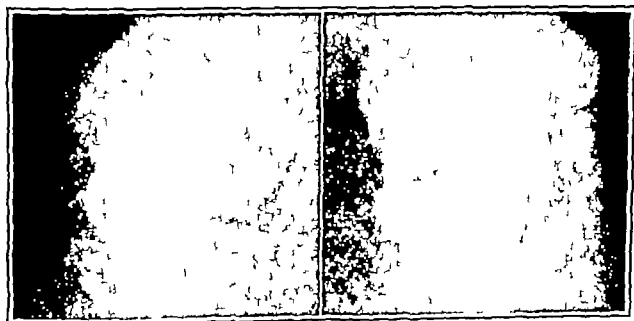


FIGURE 4 *Bilaterally Symmetrical Pseudo-fractures of Both Radial Necks*

did not reveal any renal abnormality. Examination of the gastrointestinal tract, including the small intestine, was within normal limits.

During the past year the patient has undergone intensive laboratory study without any diagnostic findings. Repeated hematologic studies were within normal limits. The last

Many examinations, however, were negative for sugar. Fasting blood sugars ranged at various times from 75 to 85 mg. per 100 cc. and glucose tolerance tests were negative. The last such test performed showed a fasting blood sugar of 82 mg. per 100 cc. with a rise to 152 mg. in 1½ hours and a decline to 97 mg. in 1½ hours and to 88 mg. in 2 hours.

Benedict's test, however, was ++++ for glucose after the control. This was repeated, and practically the same results obtained, indicating a low renal glucose threshold. The serum alkaline phosphatase ranged from 5 to 15 Bodansky

hydrochloric acid values of 39, 14, 40, 53 and 30 clinical units. The total serum protein on the last examination, which was typical of the others, revealed 6.34 gm per 100 cc., with 4.9 gm of albumin and 1.43 gm of globulin. Repeated

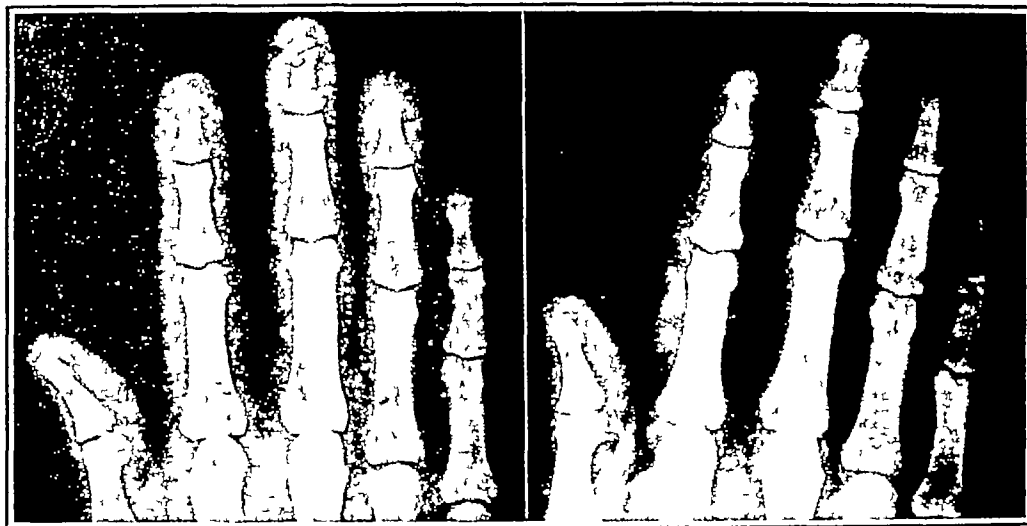


FIGURE 5 Roentgenograms of the Fingers of the Left Hand

The film on the left shows only mottled osteoporosis. That on the right, taken two months later, shows a well developed Looser's line through the base of the distal phalanx of the middle finger.

units, the last such examination on July 18, 1946, revealed 14.7 Bodansky units—a slight elevation. The serum acid phosphatase was within normal limits. Various determina-

examinations of the feces showed no starch granules, no increase in the fat content and negative examinations for occult blood and parasites or ova. Basal metabolic rates

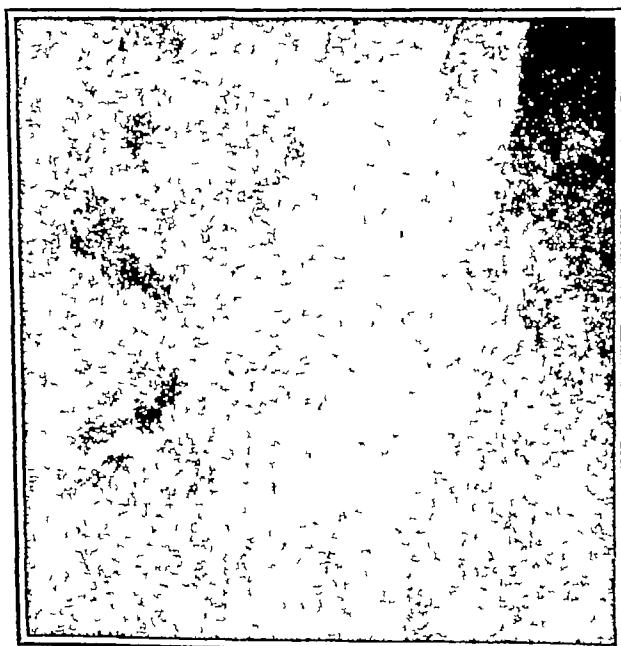


FIGURE 6 Pseudofracture of the Left Ilium Extending across the Superior Portion of the Acetabulum

tions of the serum cholesterol and cholesterol esters were normal. Repeated examinations of the urine for Bence-Jones protein were negative. The icteric index was normal, as were the cephalin-flocculation and bromsulfalein tests. A fractional gastric analysis with histamine revealed free



FIGURE 7 Fracture of the Neck of the Right Femur, with a Coxa-Vara Deformity

were obtained at varying intervals and ranged from -11 to +13 per cent. The Congo-red test was negative.

Extensive and repeated calcium-balance studies were obtained over an 18-month period without revealing significant results. In various laboratories and at various times during this interval the blood phosphorus ranged from 1.6 to 3.8 mg per 100 cc., and the calcium values ranged from 8.8 to

11.8 mg per 100 cc. Between the extremes numerous normal values were obtained, and repetition of the chemical studies always resulted in further normal values on the follow up examination.

Special studies were done after the patient had been placed on a diet containing approximately 0.1 gm. of calcium daily for 2 weeks. The serum alkaline phosphatase was 11.7 Bodansky units, the serum acid phosphatase 0.1 Bodansky unit, the serum phosphorus 2.15 mg., and the serum calcium 9.9 mg per 100 cc., the 24-hour fecal phosphorus was 64.8 mg., the 24-hour fecal calcium 304 mg. the 24-hour urine phosphorus 761.6 mg., the 24-hour urine calcium 112 mg., and the 24-hour urine 17 ketosteroids 10.8 mg.

Studies of the blood chloride, uric acid and blood urea nitrogen were within normal limits. The blood phosphatase was slightly elevated on most examinations, and the phosphorus content of the serum was at the lower limits of normal.

Repeated electrocardiograms were within normal limits. A biopsy from the right tibia on May 2, 1945 revealed no areas of fibrosis, and the segment of cortex appeared thin. The Haversian canals were extremely large, and a diagnosis of rarefied bone was made. Biopsy of the skin over the pigmented area on the left leg was reported to show hyperpigmentation of the skin with atrophy.

For 1½ years the patient's condition changed little. There was some progression of the x-ray changes but the general physical condition remained unimpaired. From time to time the patient had greater degrees of pain in the lower back, right hip and legs. He was seen by various orthopedic consultants, who believed that no orthopedic treatment was indicated for the shortening of the right leg. Treatment with large amounts of various preparations of vitamins D and A, of calcium given both orally and parenterally of multiple vitamins and of high caloric and high vitamin diets did not result in any change in the bone condition. The patient gained weight during hospitalization and had no complaints other than the difficulty in walking. He was able to walk short distances with a cane but had difficulty in getting out of bed unaided and in arising from the sitting position. Physiotherapy afforded some symptomatic relief of pain.

This case is considered to fall within the criteria for the diagnosis of Milkman's syndrome. The various conditions in which pseudofractures occur were satisfactorily eliminated, both clinically and by laboratory means. This case, in which the patient presented thirty-nine fractures, is typical of the chronicity of the condition. Autopsy has been reported in only 1 case, after eight years of observation, and nothing of pathognomonic value was found on histologic study.<sup>2</sup>

The case reported above is somewhat unique in that it occurred in a male, only 1 similar case having been reported.<sup>6</sup>

Camp and McCullough,<sup>7</sup> in a learned discussion of pseudofractures, point out the varied and diverse diseases affecting the skeletal system in which such lesions occur, and deny the existence of this distinct clinical entity. In the diseases listed by them, however, careful clinical study would ordinarily lead to a definitive diagnosis, since the pseudofractures are but a minor finding in these conditions. In the group of cases under discussion as Milkman's syndrome, the obvious features of the disease in differential diagnosis listed by Camp and McCullough are absent and what remains is a distinct syndrome of unknown etiology.

### SUMMARY

A case of Milkman's syndrome occurring in a male is reported.

A brief review of the literature and differential diagnosis is presented.

Subsequent to the preparation of this paper Albright and his associates,<sup>8</sup> in a presentation wealthy in metabolic data, conclude that Milkman's syndrome is a form of osteomalacia, underlying which there may be various etiologies. Emphasis is placed on osteomalacia resulting from a specific form of renal acidosis tubular insufficiency without glomerular insufficiency. They too disagree with Camp and McCullough and believe that the ribbon-like zones of decalcification called "pseudofractures" by some authors are found only in Milkman's syndrome and are consistent with underlying osteomalacia. The various etiologies listed in this article explain why therapy must necessarily differ to be efficacious in all cases of Milkman's syndrome.

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## MEDICAL PROGRESS

### CHEMICAL FACTORS IN ASTHMA\*

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**K**NOWLEDGE of what takes place within the patient during a paroxysm of asthma or during an attack of urticaria is not at all clear. Such simple matters as the balances of water, salt or acids and bases have been observed in asthma and in other so-called "allergic diseases," but few of the studies are sufficiently controlled to establish any definite conclusions. The fact is that the available data are often conflicting and therefore confusing. For example, some practitioners treat their patients by withholding salt and water, and others by administering salt and water by mouth and by vein, each group claiming good clinical results. Acids are given sometimes in large amounts, and good effects are reported from the treatment, alkalies are given by other authors, apparently with similar success. The feeding of potassium is advised in some cases, and the injection of calcium in others. Vitamins are administered in the hope that the extra quantities will be beneficial.

It is quite evident that present impressions derive almost entirely from clinical observations. Good experiments, carefully devised and carefully executed with proper controls, are mostly lacking. If patients are to be treated with uniform success, the rationale of treatment must be understood—the physiologic reasons as well as the clinical indications for the different procedures and the results that can be expected must be known. Before these matters can be investigated, a review of the literature is necessary, and since the literature is voluminous and is not without clinical interest, the published papers that have a bearing on this are discussed.

#### THE ACID-BASE BALANCE

In 1928 Crip and McElroy<sup>1</sup> observed that some cases of urticaria improved following the administration of dilute hydrochloric acid. By the Rehfuess technic the gastric contents of 65 healthy medical students and of 50 patients suffering from asthma or other allergic conditions were examined, a complete lack of hydrochloric acid in 36 per cent and a hypoacidity in another 32 per cent being reported. The authors concluded that a low gastric acidity, although not constant in allergy, was much more frequent than in normal persons. In 1930 Beckman<sup>2</sup> considered "potential alkalosis" a causative factor

in allergy. By this he meant that the allergic person tended to store up too much alkali or to neutralize too effectively the acid substances produced during normal metabolism, and he cited the low incidence of allergy in patients with diabetes, starvation, pregnancy and acute infectious diseases, in all of which he claimed that there was a tendency to acidosis. He stated that the allergy improved when the patient was rendered more acidotic, as by treatment with calcium, whisky and acetylsalicylic acid or mineral-acid therapy. Beckman treated 237 cases of hay fever with nitrohydrochloric acid (4 cc of a 15 per cent aqueous solution four times a day) and obtained improvement in 65 per cent. Unfortunately, he did not present any figures to show the degree of acidosis, and in the cases that improved under acid treatment he did not mention environment, weather or pollen counts, which might also have explained the good result.

In 1936 Loveless<sup>3</sup> studied the gastric contents of 138 children and adults with allergic diseases an hour after the ingestion of an Ewald meal. In contrast to Beckman, she could not find any significant deviation from the normal level of gastric acidity, nor did intensive hydrochloric acid therapy—4 cc of dilute hydrochloric acid (USP) three times a day—influence the acid-base balance as shown by the bicarbonate-tolerance test and by studies of the plasma carbon dioxide content. The alkali reserve was not lowered to any appreciable extent. Clinical results on the patients receiving intensive acid therapy did not show any beneficial effects.

Evidently, then, potential alkalosis is not a constant factor in patients with allergy. On the contrary, the poor pulmonary ventilation in asthma causes a retention of excess carbon dioxide in the blood and a compensatory rise in the plasma bicarbonate level. When a nonvolatile acid like hydrochloric acid is administered it will combine with the bicarbonate, releasing carbon dioxide, and the chloride will be excreted by the kidneys. If the excess carbon dioxide can then be eliminated by the lungs, all will be well, if not, dyspnea may become increased, for it is the accumulation of carbon dioxide, as well as the anoxemia, that causes the distress in these patients. If alkali is administered it will compensate for the excessive carbon dioxide for a time, and the normal ratio between carbonic acid and bicarbonate will be established at a higher level. Eventually, however, a limit is

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reached the lungs cannot blow off more carbon dioxide, the kidneys cannot take care of the base, and meanwhile the excessive carbon dioxide in the blood diminishes the content of oxygen. Dyspnea increases dangerously, the treatment may thus do harm.

#### SODIUM, POTASSIUM AND WATER BALANCE

It is well known that sodium potassium and chloride are vital to the regulation of the normal intracellular fluid electrolyte balance. Most of the sodium and the chloride ions are contained in the plasma of the blood and in the interstitial fluids, whereas most of the potassium resides in the tissue cells. Potassium leaves the cells when their membrane permeability is altered, or when increase of acid in the blood draws base from the inside of cells. Thus, muscular activity causes a movement of potassium from cells into the body fluids. Potassium is also lost from cells when there is a loss of total salt and water, as in hemorrhage or burns. Trauma, intestinal obstruction, severe infections and Addison's disease, which cause a loss of body sodium, pull out cellular potassium. In hypertension or after an injection of adrenalin, there may be an increase of serum potassium. It is also known that an infusion of sodium chloride or stimulation of the central vagus nerve will result in an increase of serum potassium. Sodium and potassium ions tend to increase neuromuscular excitability, and potassium is said to be concerned with the release of acetylcholine at nerve endings.

The normal level of potassium in the blood ranges between 3 and 5 milliequiv per liter. In 1927 Klyn<sup>4</sup> first called attention to abnormally high levels of potassium in the blood serum of asthmatic patients, he found an average value of 6.5 milliequiv per liter in 40 patients. Unfortunately, Unshelm,<sup>5</sup> in 1929, and Lierle and Sage,<sup>6</sup> in 1932, could not repeat his results; they reported normal levels of 5 milliequiv per liter. In 1937 Rusk and Kenamore<sup>7</sup> claimed that potassium therapy was indicated in urticaria, stating that potassium metabolism was markedly altered in skin inflammation and irritability, and that an increase in skin potassium caused an appreciable decrease in localized irritability. They pointed out that potassium is similar to adrenalin in its pharmacologic action. In 6 patients with chronic urticaria a high-protein, low-sodium, acid-ash diet was used, with 4 to 6 gm of potassium chloride added daily, and good results were obtained. No laboratory figures to support the theory were presented, however, and the number of cases was too small for any definite conclusions to be formed. In the same year Wenner and Buhrmester<sup>8</sup> reported the liberation of an acetylcholine-like substance in rabbits during anaphylactic shock, which they thought was caused by the marked increase in serum potassium that they found. They admitted that the specific action of potassium on

the vegetative nervous system was extremely uncertain.

In 1938 Cohen,<sup>9</sup> following the suggestions of Rusk and Kenamore,<sup>7</sup> treated 8 cases of chronic urticaria with a high-protein, low-sodium, acid-ash diet with added potassium chloride, but he did not find improvement in any case. Bloom<sup>10</sup> thought that allergy might be basically an endocrine dysfunction with secondary disturbances of electrolyte metabolism. He treated 29 cases of hay fever with 0.3 gm of potassium chloride three times daily, and obtained good results, a few cases of eczema, nasal polyposis, acute urticaria, chronic allergic sinusitis and migraine also improved under the same therapy. Patients with chronic urticaria were not benefited. It is difficult to see how such a small dose of potassium chloride could alter the body electrolyte balance, the author did not present any laboratory studies, nor did he mention other variable factors that influence hay fever, such as atmospheric conditions and environment. Rusk, Weichselbaum and Somogyi<sup>11</sup> reported serum potassium levels above normal in 20 patients with urticaria and in 10 patients with bronchial asthma. They postulated that potassium was released from the cells and that, if an excess of potassium was fed, the cellular loss would be replaced and the symptoms would be improved, some patients so treated obtained relief.

This new idea of treatment with potassium drew a variety of papers from American clinics. Using approximately 1 gm of potassium chloride daily in various numbers of patients with allergic disorders, Harley,<sup>12</sup> Harsh and Donovan,<sup>13</sup> Rubin and his associates,<sup>14</sup> Engelsheer<sup>15</sup> and Furstenberg and Gay<sup>16</sup> could not produce any appreciable benefit. Abt<sup>17</sup> obtained good results in patients suffering from hay fever and asthma, but his therapy with potassium chloride was given in October after the hay-fever season was over. Parker<sup>18</sup> reported that persons with asthma, hay fever or vasomotor rhinitis who received potassium chloride or potassium gluconate were generally benefited.

Reports on the influence of sodium and water on patients with asthma and allied disorders are also numerous. Pitressin, the antidiuretic principle of the pituitary gland, causes not only a retention of body water but also a coincident absolute increase in the output of sodium and of chloride in the normal subject. Cook and Stoesser<sup>19</sup> believed that this action offered a unique opportunity to dissociate the effects of water and salt in the asthmatic patient; they gave 6 asthmatic children a low-sodium diet and also Pitressin in doses of 0.3 to 0.5 cc. every three hours for eight doses, or until there was a gain in weight due to the water retention, and when this occurred the asthma improved. Acute symptoms developed in 1 case when a dose of 0.6 gm of sodium chloride was given. The authors suggested that the sodium ion exercised an adverse influence,



on the asthmatic patient, independent of its usual relation to hydration

In 1939 Sheldon, Howes and Stuart<sup>21</sup> speculated on the relation of general body water and sodium to the local tissue edema occurring in allergic disease. They studied water and sodium metabolism in 5 asthmatic patients, measuring carefully the diets, intake and output. They found that, during prolonged asthmatic attacks, there was a definite loss of body water and sodium. In the following year Stoesser and Cook<sup>22</sup> reported further investigations. In 12 asthmatic children they varied the electrolyte metabolism by different procedures and found no consistent changes in the levels of potassium, chloride or sodium in the blood serum. In some cases they observed remissions when the patients were given a diet with low-salt content and at the same time were treated with artificial fever, but asthma recurred when 1 or 2 gm of sodium chloride was added to the diet. In other cases, when 6 to 10 gm of potassium chloride daily was added to the low-sodium diet, mild attacks of asthma ceased, but the severer ones continued, when the potassium chloride was discontinued, the latter ceased. The authors concluded that the amounts of sodium, potassium and chloride in the diet were of importance in the control of bronchial asthma occurring in children, but they did not explain the reason for the beneficial effect of either the restriction of sodium chloride or the administration of potassium chloride.

Further studies on changes in serum sodium concentration in allergy were made in 1940 by Donovan and Harsh,<sup>23</sup> who determined the serum sodium concentrations of 50 patients suffering from asthma, urticaria or allergic rhinitis and of 133 persons who gave no personal or family history of allergy. The concentrations of both patients and controls fell within normal limits, and the authors concluded that there was no evidence of a direct connection between the allergic symptoms and the concentration of sodium in the serums of the allergic patients. In 1940 Kern,<sup>24</sup> discussing water balance in allergy, presented the theory that changes in the water balance of the body influence the occurrence of allergic phenomena. His statement was as follows:

Water and salt retention will favor the development of allergic reactions. Dehydration and salt loss will antagonize allergic reactions. Increased intake of sodium, by tending to increase interstitial fluid and edema, will also favor the development of allergic reactions. Increased intake of potassium or decreased intake of sodium, will antagonize allergic reactions. Such shifts of water balance occur clinically in a variety of conditions, or they may be induced by a number of therapeutic measures. But the effect of hydration and dehydration on allergic reactions is purely nonspecific, and consequently the causes initiating changes in water balance must not have attributed to them any specific etiologic significance in the causation of the allergy itself.

In 1941 Kinsell and Zwemer<sup>25</sup> attacked the problem by another method. They studied the

level of potassium in the blood of guinea pigs in anaphylactic shock. They sensitized 34 animals with 0.25 cc of horse serum, and gave the second (shock) dose intraperitoneally one to four weeks later. In animals in which anaphylactic shock of rapid onset and marked intensity was produced, they observed a definite rise in plasma potassium, which was greater than could be accounted for by the hemoconcentration, as measured by the red-cell volume and the plasma protein. This was in contrast to the control group, which showed hemodilution, lowered plasma protein and, in some cases, lowered potassium. The authors did not understand the mechanism of the rise in potassium, but they assumed that there was a loss of potassium by cells due to either a change in cell-membrane permeability or a disruption in the hypothetical intracellular potassium colloid complex, or both. Since injections of potassium salts produce many symptoms of shock, these findings suggested that the use of large amounts of potassium in allergic conditions was contraindicated rather than indicated.

In the same year Sullivan<sup>26</sup> was doubtful whether potassium and calcium influenced the local water balance by physicochemical changes or by pharmacologic effects on the nervous system. He treated 29 patients — mostly asthmatics — 13 with 25 per cent potassium chloride solution and 16 with calcium gluconate. Neither group experienced any marked degree of relief of symptoms, and in neither group did the levels of calcium, potassium and chloride in the blood show any deviation from normal values.

In 1942 Stoesser,<sup>27</sup> who had studied the effects of potassium therapy in children with asthma, turned his attention to infants with eczema. It had been shown by Holt and others that infants had a higher content of water and of sodium chloride and a lower potassium-sodium ratio than older children; these features disappeared with growth, but in the child with eczema the disappearance was slow. Stoesser gave 4.0 gm of potassium chloride daily to some of his eczematous infants. During the acute eczema the serum potassium level was above normal both in the treated infants and in the untreated eczematous cases, but when the oozing subsided the values for potassium became normal in both groups. Meanwhile, the serum sodium and chloride were normal in all cases and during all stages of the eczema. The author concluded that there was a marked disarrangement of the normal electrolyte balance, that in eczema the threshold for excretion of potassium was raised so that the tissue cells had a high content of potassium and that therapy with potassium chloride was therefore not indicated.

In 1942 Harsh and Donovan<sup>28, 29</sup> studied 12 asthmatic children. At first they fed a diet normal in sodium but high in potassium, with the daily addition of 7.5 gm of potassium chloride, and found little change in the asthma. When, however, they fed a diet normal in potassium but high in

sodium, with 60 gm of sodium chloride added daily, the children were worse, and, furthermore, the blood potassium was even higher than it had been on the high-potassium diet. The blood sodium, on the other hand, was lower than that in the non-allergic children on the same diet, and more sodium was excreted in the urine.

In 1939 Rubin and Rapoport<sup>20</sup> had claimed that injections of potassium chloride with restriction of sodium protected guinea pigs from a shock dose of antigen. To confirm this evidence, Carlson and Whitehead<sup>21</sup> sensitized guinea pigs with sheep serum and determined the minimum lethal dose of the antigen. When they administered the shock dose of the antigen they gave at the same time sodium thiosulfate, potassium chloride or potassium thiosulfate. They found that sodium thiosulfate showed no inhibitory effect on the anaphylactic reaction, but that potassium, either chloride or thiosulfate, afforded protection against the minimum lethal dose of antigen. From previous observations in their clinic Stoesser and Booth<sup>22</sup> had assumed that the depletion of body sodium, however produced, relieved the symptoms in patients with asthma. They then subjected children with chronic asthma to various other forms of therapy. To one group they administered 2 to 12 gm of potassium chloride daily and kept the sodium and chloride intake constant. This treatment produced a diuresis with loss of sodium, and there was an apparent improvement in the asthma. To another group they gave 1 to 10 gm of sodium chloride, 8 to 20 mg of desoxycorticosterone acetate and 8 cc. of adrenocortical extract each day. Like Harsh and Donovan, they noted that with the retention of sodium and the excretion of potassium the symptoms of asthma increased in severity.

From the above it is obvious that the literature contains evidence concerning the roles of potassium, sodium and water in allergy that is confusing if not conflicting. Some workers (Rusk,<sup>7</sup> Bloom<sup>10</sup> and Parker<sup>18</sup>) claim improvement of patients with allergic conditions by potassium therapy. Others (Cohen,<sup>9</sup> Harley,<sup>12</sup> Harsh and Donovan,<sup>13</sup> Rubin,<sup>14</sup> Engelsber,<sup>15</sup> Furstenberg<sup>16</sup> and Sullivan<sup>17</sup>) find no appreciable benefit from such therapy. Stoesser and Cook<sup>19, 20, 21</sup> claim that asthma is aggravated by retention of water and sodium. In our clinic patients with severe asthma who become dehydrated and who improve after administration of water and sodium chloride (isotonic solution) are seen. So far, it can be concluded only that any marked shift in water balance one way or the other may aggravate or improve asthma. There is no evidence that changes in electrolyte and water balance are specific or that they are a fundamental factor in the symptom complex.

#### CALCIUM, PHOSPHORUS AND MAGNESIUM

Another drug formerly used with some enthusiasm in the treatment of asthma is calcium, which has

an effect on nerve and muscle irritability. Whereas an excess of total calcium has little effect on the function of the nervous system, a reduction in ionized calcium excites the peripheral and central nervous systems. Calcium deficiency affects primarily the peripheral neuromuscular mechanism. Bronk and his associates<sup>23</sup> have shown that autonomic ganglion cells are stimulated by a decrease in calcium concentration so that the cells are more readily excited by acetylcholine, whereas an increase of calcium blocks transmission. In addition, it is stated that calcium decreases the permeability of capillaries, although there is little experimental evidence in support of this contention. Because of their effect on ganglions and capillaries, calcium salts have been widely used for the control of inflammation and edema in asthma, urticaria and angioneurotic edema. Unfortunately, the use of calcium in practice has not supported the theory.

Tainter and Van Deventer<sup>24</sup> tested the effect of calcium lactate on the experimental edemas produced in rabbits and cats by such drugs as paraphenyldiamine and mustard but could not demonstrate any protective action.

In 1928 Crip and McElroy<sup>1</sup> determined the blood calcium level in patients with asthma, urticaria or angioneurotic edema. In a group of 40 nonallergic persons the normal value was observed to be 10.43 mg per 100 cc. In 80 patients with asthma the total blood calcium was 10.08 mg, in 43 cases of hay fever it was 10.55 mg, in 21 cases of urticaria 9.66 mg, and in 2 cases of angioneurotic edema 10.40 mg per 100 cc. Their conclusions were that a deficiency of calcium does not exist in atopic conditions, that calcium therapy, as lactate given in doses of 5 gm three times daily for twenty days with parathyroid extract, has little if any influence on the blood calcium of allergic patients, and that the rationale of calcium therapy, because some allergic patients improve after intravenous administration of calcium, is based on the idea that calcium depresses all tissues, especially the nervous system, and tends to lessen the permeability of tissue cells and thus to reduce transudation, which is a frequent manifestation in the shock organs of allergic patients. Sterling<sup>25</sup> found normal blood calcium levels in 62 of 85 allergic patients, and blood phosphorus levels below the normal, which he called 3.0 to 4.5 mg per 100 cc, the method of determination not being reported. He claimed a marked symptomatic improvement in a high percentage of patients who were "put on phosphorus," and his theory was that the offending allergens were converted into harmless substances by enzymes activated by the phosphate. This theory has not been substantiated, and successful treatment with phosphorus has not been reported by others.

In 1929 Greenberg and Gunther<sup>26</sup> thought that a study of the diffusible calcium might give different results from those of total blood calcium in allergic persons. They analyzed the bloods of 14 patients

with various allergic disorders, and found that the diffusible calcium varied between 40 and 56 mg per 100 cc, their figures for nonallergic adults varied from 45 to 60 mg per 100 cc. In their cases the total and diffusible calcium of the blood serum varied together and within the normal range. Cantarow,<sup>37</sup> however, found a definite and quite constant increase in the ratio of diffusible to non-diffusible calcium in the blood in 25 cases of bronchial asthma, and he considered the disturbance of calcium balance to be related to the increased capillary and cellular permeability that was believed to exist in bronchial asthma and allied disorders.

Ramirez<sup>38</sup> picked 50 patients with asthma, 50 with hay fever and 50 with urticaria in whom the levels of blood calcium were less than 10 mg per 100 cc. If calcium could help allergic patients, it should have done so in this group. After calcium therapy the levels of calcium in the blood were slightly increased, but there was little clinical improvement. Kern and Teller<sup>39</sup> showed that blood calcium was normal (9 to 11 mg per 100 cc) in nearly all of 88 cases of asthma—both allergic and “infectious.” Lierle and Sage<sup>6</sup> also found normal levels of calcium and phosphorus with normal serum protein concentrations in the bloods of 20 asthmatic patients. In 1931 Crandall and Feinberg<sup>40</sup> observed the average level of serum phosphorus to be 3.57 mg per 100 cc in 75 allergic patients. In contrast to Sterling<sup>35</sup> they concluded that the level of inorganic phosphorus in the serum of the fasting allergic person was within normal limits.

Magnesium is essential for the functional integrity of the neuromuscular system—it blocks muscular contraction, produces a true depression of the central nervous system and has a local anesthetic action on peripheral nerves. It also causes respiratory failure when used as a depressant, the fact that this can be relieved by administration of calcium indicates an antagonistic action of the two drugs.

In 1938 Braden and Braden<sup>41</sup> studied the levels of magnesium in the blood serum of 30 patients with allergic symptoms and found the values to be well within the range of normal variation. Haury,<sup>42</sup> observing that anaphylactic shock in sensitized guinea pigs could be prevented by raising of the serum magnesium before the test injection, analyzed the blood of 66 patients suffering with bronchial asthma. Half the patients with acute asthma showed low values for serum magnesium. He concluded that a deficiency of the magnesium ion was a contributing factor in asthma by upsetting the neuromuscular mechanism but that hypomagnesemia was by no means an essential etiologic factor. Two of his patients, at the height of an asthmatic paroxysm, were given 20 cc of 10 per cent magnesium sulfate intravenously and 4 cc of a 50 per cent solution of the same drug intra-

muscularly, and were relieved for approximate twenty-four hours.

Thus, according to the majority of workers, it is evident that there is no important disturbance of calcium, of phosphorus or of magnesium metabolism in allergic patients. Treatment with these compounds is certainly not specific. As outlined above, if it does good at all, the mechanism can depend only on the pharmacologic effect of these substances on the neuromuscular mechanism.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 33361

#### PRESENTATION OF CASE

A fifty-nine-year-old schoolteacher was admitted to the hospital because of jaundice and malaise.

About a month before admission the patient had begun to notice slight nausea. Two weeks later severe malaise and increasing weakness appeared, and ten days before admission, jaundice, light stools and dark urine were noted. The jaundice increased, becoming severe, until two days before entry, when it seemed to decrease, but without change in the urine or stools. The patient had had chilly sensations but no real shaking chills, and she had felt hot. There was no pain or abdominal tenderness, the appetite had decreased somewhat, and she had lost 7 pounds in the last ten days. There was no history of exposure to other jaundiced people or chemicals or of alcoholism. There was some intolerance to greasy foods.

The past history revealed that at the age of thirty-five, at about the fourth month of pregnancy, an appendectomy had been performed in this hospital. The patient was readmitted fourteen years later because of epigastric pain of a year's duration, associated with frequent eructations and regurgitation of food. Five weeks prior to that admission, she had vomited about half a cupful of blood, and she had subsequently vomited small amounts of blood on four or five occasions. X-ray films at that time revealed a hiatus hernia involving about a fourth of the stomach. The left phrenic nerve had been crushed, with subsequent improvement of the symptoms. The diagnosis at that time was asymptomatic cholecystitis. Another x-ray film on discharge revealed no hiatus hernia. Subsequently she was

well for seven or eight months, after which the symptoms recurred. Despite difficulty in swallowing the patient maintained her weight at about 170 pounds. Additional information revealed joint pains, thought to be rheumatic fever, forty years previously and a vaginal repair twelve years previously. Also, for the past fourteen years, she had had occasional attacks of dyspnea, especially on exertion, associated with sharp precordial pain and relieved by rest.

Physical examination revealed a well developed, obese, markedly jaundiced woman with a perforated nasal septum and large submaxillary, axillary and supraclavicular lymph nodes. The heart and lungs were normal. The abdomen showed an area of local tenderness in the right upper quadrant. The cervix was absent, and there was a firm nodule in the left vaginal vault. The left knee was enlarged and stiff, and the left ankle was ankylosed. The right second metacarpal phalangeal joint was enlarged. There was slight edema of both shins, and varicose veins bilaterally, with discoloration around the left medial malleolus.

The temperature was 100.6°F, the pulse 80, and the respirations 20. The blood pressure was 150 systolic, 80 diastolic.

Examination of the blood revealed 11 gm of hemoglobin and a white-cell count of 8000, with a normal differential count. The urine had a specific gravity of 1.010 and gave a +++ test for albumin and a +++ test for bile. The sediment contained innumerable white cells. A stool was clay colored and guaiac positive. X-ray examination revealed clear lung fields, a slightly enlarged heart in the left ventricular region and a tortuous aorta. The abdomen contained several areas of calcific density, overlying the region of the gall bladder, that resembled laminated gallstones. The liver and spleen were not enlarged. A barium enema showed numerous diverticula from the distal transverse colon to the rectosigmoid. A gastrointestinal series disclosed a large hiatus hernia, at times ballooning out to more than 5 cm in diameter and causing considerable obstruction of the passage of barium through the cardia of the stomach, which lay above the diaphragm, with the result that the esophagus ballooned out to more than 5 cm in diameter before it emptied into the hernia. A 1-cm. crescentic defect along the lesser curvature of the antrum, just at the pyloric area was thought to be a small

polyp, an aberrant pancreas or an anomalous mass of rugae (A similar finding had been noted ten years previously) The prothrombin time was normal The van den Bergh reaction was 14 mg per 100 cc direct and 20 mg indirect The total protein was 6.3 gm per 100 cc, with 3.3 gm of albumin and 3.0 gm of globulin A cephalin-flocculation test was ++++ in twenty-four and forty-eight hours The cholesterol was 175 mg, and the nonprotein nitrogen 20 mg per 100 cc

An operation was performed on the ninth hospital day

#### DIFFERENTIAL DIAGNOSIS

DR WYMAN RICHARDSON Does anyone know whether this woman did hair dressing on the side?

DR DANIEL S ELLIS I do not know

DR RICHARDSON X-ray films revealed a hiatus hernia involving about a fourth of the stomach That is sufficient to account for the bleeding

The statement that there were large submaxillary, axillary and supraclavicular nodes is not accurate How large is "large?" Were the nodes 7 or 8 cm in diameter, were they easily palpable, and were they movable or soft and rubbery? Regarding the diagnosis in this case, one must know whether or not to take that description seriously The word "large" should make one take it seriously I should still like to know if anyone can tell me how large is "large"

DR TRACY B MALLORY Do you know, Dr Dahl?

DR LEWIS K DAHL According to Dr Richardson's classification the lymph nodes would not be regarded as large They were barely palpable

DR RICHARDSON Apparently they were not taken seriously

"The cervix was absent, and there was a firm nodule in the left vaginal vault" I do not know how to account for that either

The temperature of 100.6°F represents fever, if taken by mouth, if by rectum, it is hardly worth talking about I assume that it was rectal because most admission temperatures are

A hemoglobin of 11 gm is not normal for any patient The red-cell count is not recorded I should have liked to see the smear One can tell a great deal from a blood smear, and the observer should have noticed whether there were so-called "liver-failure cells" or "virus lymphocytes" That would be a great help in differential diagnosis

The total protein was within normal limits There was a definite increase in globulin, so that the ratio was close to 1 I should like to see the x-ray films of the stomach and cardia, to determine whether or not a carcinoma near the cardia accounted for the lymph nodes

DR STANLEY M WYMAN This is a film of the chest showing the enlarged heart, prominent chiefly in the region of the left ventricle, and the tortuous aorta The lung fields are not remarkable The

calcification described in the right upper quadrant is seen best in these two films and has the appearance of several laminated stones lying in the region of the gall bladder There is some gas close to the stones that appears to lie within a viscus I suspect that it is the duodenal cap The barium enema shows diverticulums, without significant spasm The gastrointestinal series shows the widened esophagus and the hiatus hernia from this point upward, without undue prominence of the mucosal markings but with delay in opening of the esophagus The proximal portion of the stomach is not remarkable otherwise, except for the immediate prepyloric region, where a round filling defect is seen It is present in all films and well seen in these two spot films It is a lobulated, approximately 1-cm mass, and from the record it was apparently present ten years previously, although I do not have the old film for comparison

DR RICHARDSON Is there any evidence of an obstructive lesion other than the hernia to account for the esophageal dilatation?

DR WYMAN No

DR RICHARDSON These stones are small enough to have gotten into the common duct

DR WYMAN I cannot see any others scattered around, however

DR RICHARDSON The operation might have been a biopsy of one of the nodes, a trocar biopsy of the liver, a peritoneoscopy or a laparotomy I doubt the wisdom of doing a laparotomy on a patient of this sort for the reasons presented below We know that she had gallstones, and it would be easy to come to the conclusion that she also had a stone in the common duct

Regarding the onset of the disease, it seems to me that it was not typical of simple obstructive jaundice She had both nausea and vomiting, although these symptoms lasted longer than those in the average infectious case, and she had chilly sensations and may have had a fever, which does not strike me as being the typical type of Charcot fever that people sometimes have with biliary infection associated with gallstones One would expect with the onset of a gradually obstructing lesion of the biliary tract that the nausea and vomiting would have occurred later and the jaundice earlier There is some question whether the jaundice decreased, but we can take that with a grain of salt, we have no real data on that point What other evidence have we regarding the cause of this jaundice? We can assume that it was not hematogenous, because in such a case, one would expect some impression of hemolytic anemia from the smear, although I do not know that one can count on that Also, the van den Bergh reaction was not that of hematogenous jaundice, and there was bile in the urine The blood chemical findings help somewhat There was an increase in the globulin One would not expect an upset of the liver chemistry in a

straight obstructive jaundice of short duration. I have always criticized the cephalin-flocculation test, but in this case it is rather suggestive evidence of intrahepatic disease as opposed to biliary obstruction. On the basis of this evidence I shall say that the jaundice was not due to biliary obstruction by a stone or by a carcinoma of the head of the pancreas, the usual cause of biliary obstruction in people of this age, or to biliary carcinoma secondary to gallstones. The jaundice must therefore have been due to either infectious or toxic hepatitis. The reason I asked about the hair dressing is that there may be something in the material used in the so-called "cold wave" that will produce a granulopenia, and in some cases toxic hepatitis. In spite of the patient's age—infectious hepatitis seldom occurs in this age group—I believe that this disease was the most probable cause of the jaundice. Jersild\* has reported from Denmark a series of cases of hepatitis occurring exclusively in women, usually after the menopause.

I shall say that this patient had infectious hepatitis, in which enlargement of the lymph nodes is not rare and may become so prominent, with such an abnormal blood picture, that the disease is considered to be infectious mononucleosis, with jaundice, rather than infectious hepatitis with lymphadenopathy. Some patients have a positive heterophil reaction, and such cases are called infectious mononucleosis with jaundice. This patient was too old for that.

Were the enlarged lymph nodes part of the infectious-hepatitis process? When I first went over the record I was going to take the nodes seriously and consider the possibility that this patient had carcinoma in the hiatus hernia or near the cardia of the stomach, metastasizing to the lymph nodes in the neck. But since no more attention was paid to them, I shall discard that diagnosis.

Were the nodes due to some form of lymphoma, with hepatic involvement? In my experience hepatic involvement with jaundice is almost always a late manifestation of this disease, and there is rarely a primary involvement of the liver by lymphoma. I recall one case, however, in which that was the cause of rapidly progressive jaundice and death, but such a course seems unlikely in the case under discussion. I must therefore put the nodes down to a probable infectious process and shall not emphasize them further. I might say parenthetically that I have not been given a report of the blood Hinton test, and with the perforated septum one must consider the possibility of syphilis. This does not sound like *hepar lobatum* or the secondary stage of syphilis, and I think that we can safely discard that diagnosis.

We must account for the pyuria and the albuminuria. There was nothing in the way of symptoms to accompany them.

DR MALLORY: Seven years before admission the blood Hinton reaction was negative.

DR RICHARDSON: That suggests that the perforated septum was not due to syphilis.

On the basis of the pyuria and the albuminuria I shall say that the patient had chronic pyelonephritis.

The description of the joint changes sounds like that of rheumatoid arthritis, with ankylosis of the left ankle. The history of rheumatic fever was not characteristic, it may have been rheumatoid arthritis.

The cardiac symptoms might be explained on the basis of a diaphragmatic hernia. There is x-ray evidence of arteriosclerosis. One would not go astray if one said that there was a certain amount of arteriosclerotic heart disease, without committing oneself further.

I can make a diagnosis of cholelithiasis without fear of contradiction. That is the only diagnosis that I am sure is correct in this case.

The hemoglobin of 11 gm is not clearly explained, and I do not know whether or not I should take it seriously. The best way to account for it is on the basis of a mild iron-deficiency anemia associated with constant slow loss of blood from the hiatus hernia, which is not rare. I shall therefore say that this patient had infectious—possibly toxic—hepatitis, chronic pyelonephritis, rheumatoid arthritis, cholelithiasis and mild arteriosclerotic heart disease.

DR ELLIS: Was the alkaline phosphatase level determined?

DR RICHARDSON: There is no record of it.

DR MALLORY: Will you tell the impression on the wards, Dr Dahl?

DR DAHL: Unfortunately I did not see this patient until after she had been operated on. There are several points that the historian omitted from the abstract that helped Dr Richardson, I believe. Dr Peterson saw her during a period when she had what he described as typical gall-bladder colic, for which she was given Demerol with complete relief. Needless to say at that time the main diagnosis was obstructive jaundice and the attack served merely to confirm that diagnosis.

DR RICHARDSON: How about the prothrombin time? Do you remember what that was?

DR DAHL: It was slightly elevated.

#### CLINICAL DIAGNOSIS

Infectious hepatitis  
Bronchopneumonia

#### DR RICHARDSON'S DIAGNOSES

Infectious (? toxic) hepatitis  
Cholelithiasis

\*Jersild, M. Infectious hepatitis with subacute atrophy of liver epidemic in women after menopause. *New Eng J Med* 237 8-11 1947

Arteriosclerotic heart disease, mild  
Rheumatoid arthritis  
Chronic pyelonephritis

#### ANATOMICAL DIAGNOSES

*Acute infectious hepatitis*  
Bile nephrosis  
Cardiac hypertrophy  
Coronary sclerosis  
Cholelithiasis

#### PATHOLOGICAL DISCUSSION

DR MALLORY The patient was explored on one of the surgical services. The gall bladder was found to contain stones and was removed. The common duct was explored, but no stones were found in it or in the cystic duct. The common duct was drained. The liver was not considered grossly abnormal, and nothing abnormal was felt in the head of the pancreas. After operation the patient was not relieved of jaundice, slowly and steadily failed, passed eventually into a cholemic state and died twenty-four days after operation. Do you care to change your diagnosis, Dr Richardson?

DR RICHARDSON Infectious hepatitis, with atrophy of the liver.

DR ELLIS Dr Richardson is a brave man to make that diagnosis in the presence of gallstones.

DR REED HARWOOD How about cinchophen poisoning?

DR MALLORY There was no history of it.

DR RICHARDSON It used to be Weldon. That is a good suggestion in a patient with known arthritis.

DR MALLORY Post-mortem examination showed a severely diseased liver. The organ was only slightly reduced in size, weighing 1600 gm, but was extremely flabby. When it was laid on the table, it settled and flattened out, unable to maintain its form. Microscopically, such livers are troublesome because there is such extensive necrosis that it is impossible to see more than the shadow outlines of pre-existing cells. It is difficult to distinguish ante-mortem from post-mortem changes. Enough could be made out, however, to say that there was fairly extensive round-cell infiltration of the portal areas and considerable ante-mortem degeneration of the liver cells, which were frequently swollen with fat vacuoles and contained large amounts of bilirubin. There is no question that acute hepatitis was present. On the histology as it stands, I do not believe that I can distinguish between the toxic and the infectious type of hepatitis. I am inclined to agree with Dr Richardson that the infectious type is more probable, since there was no history to suggest intoxication.

The other findings at autopsy were a moderately hypertrophied heart, which weighed 450 gm, with severe sclerosis of the left descending coronary artery and some narrowing of other branches, but

no areas of infarction. The serous cavities contained small to moderate amounts of fluid—a frequent finding in liver disease. These were transudates in character. There were a diverticulum of the duodenum and numerous diverticula of the sigmoid, and there was some localized endometriosis of the uterus, which probably represented the pelvic mass that was felt.

DR RICHARDSON What about the kidneys?

DR MALLORY They were enlarged and deeply bile stained and showed the picture that is described as bile nephrosis. There was no evidence of pyelonephritis.

DR WYMAN. What was the nature of the lesion in the prepyloric region?

DR MALLORY Other than the duodenal diverticulum, nothing was noted.

DR RICHARDSON Have you seen the article by Jersild?

DR MALLORY. Yes, I have.

DR RICHARDSON This case seems similar to the group that he reported. Do you think that we are going to begin to see them here?

DR MALLORY This case is entirely analogous, as I see it. There is nothing to distinguish these cases from ordinary infectious hepatitis except the epidemiologic character. They have occurred almost exclusively in women, beyond the menopause, and the mortality rate is extraordinarily high—nearly four hundred times as high as that in ordinary hepatitis.

#### CASE 33362

#### PRESENTATION OF CASE

A forty-nine-year-old man entered the hospital complaining of epigastric pain and vomiting.

For many years the patient had had symptoms of intermittent epigastric burning and gaseous eructation, usually associated with bouts of excessive eating and drinking. X-ray studies ten years prior to admission were said to have shown a duodenal ulcer. Occasionally, he vomited after excesses but was always able to control the symptoms by limiting his diet to crackers and milk for a few days. Two years before admission he had a severe attack of nonradiating epigastric pain, with vomiting, chills and fever, this lasted a few hours and was relieved permanently by a single injection of morphine. Subsequently, the symptoms were as before, although slightly more frequent. A month before entry he began having attacks of epigastric pain and vomiting that were quite persistent and recurred at weekly intervals. These were accompanied by fever and chills, but otherwise the patient felt fairly well, without malaise or nausea. The appetite remained good. There was no evidence of bleeding in the stools or vomitus.

Physical examination was negative. The patient appeared to be in good health, without acute discomfort. The abdomen was soft and nontender. The temperature, pulse, and respirations were normal. The blood pressure was 108 systolic, 70 diastolic.

Examination of the blood revealed a hemoglobin of 12 gm and a white-cell count of 11,300, with a normal differential count. The nonprotein nitrogen was 24 mg and the total protein 6.7 gm per 100 cc, the chloride was 104 milliequiv per liter.

A gastrointestinal series showed a normal esophagus. The stomach contained a rather large amount of secretion. There were a small hiatus hernia and some spasm in the region of the antrum. There was no evidence of a crater or filling defect in the stomach. The duodenal cap filled well, without deformity. The duodenal loop was normal.

On the fifth hospital day an exploratory laparotomy was performed. The gall bladder was considerably thickened and contained stones. A stone was also palpable in the common duct. The stomach and duodenum appeared entirely normal. The liver was thought to be rather small but not particularly abnormal in appearance. The common duct was opened and found to be dilated and surrounded by considerable inflammation. A stone the size of a large bean was removed just above the papilla. The common duct was washed out with physiologic saline solution, and the papilla dilated. The gall bladder was then removed, and a probe passed down through the stump of the cystic duct to ensure the absence of stones. A catheter was sutured into the duct. The immediate postoperative condition was good. The blood pressure and pulse were stable, but the temperature rose for a single day to 102°F. The common-duct catheter did not drain properly and was thought to be plugged. Bile seeped through a draining wick in large quantities, however. On the fifth postoperative day the patient became markedly agitated, with hallucinations lasting for approximately forty-eight hours. Barbiturates were discontinued, and he improved. On the ninth postoperative day the common-duct catheter was partially out and was removed entirely. The drain was half withdrawn. All skin sutures were taken out. The wound was clean, closed and well healed. On the following day the wound suddenly became painful and hard. When examined it was red and tender and bulged in the right end. On pressure bloody fluid was discharged. The wound was opened for about 3 cm, and a dry sponge was packed into it. Later the same day the patient felt weak and nauseated, and the bandages were found to be blood soaked. The pulse was 80, the temperature 99°F, and the blood pressure 70 systolic, 60 diastolic. An exploratory operation was done, and the bleeding was found to be due to numerous areas of oozing along the wound and the drainage tract and from

the gall-bladder-resection bed. Fibrin foam and thrombin appeared to control the bleeding.

During the following two and a half weeks the patient continued to bleed in large amounts from the wound and by rectum. He often complained of severe epigastric and shoulder pain, which was aggravated by lowering of the head of the bed. The blood pressure fell to a shock level on a few occasions. The prothrombin time, which was determined on several occasions, varied from 18 to 23 seconds (normal, 15 seconds). The platelets appeared normal. The clotting time was 4 minutes in the first tube, 5 minutes in the second tube and 6 minutes in the third tube. The bleeding time was 130 seconds. On the twenty-fifth hospital day the patient became quite jaundiced. The urine gave a +++ test for bile, with urobilinogen present up to a 1:700 dilution. The van den Bergh reaction was 8.7 mg per 100 cc direct and 11.5 mg indirect.

Throughout the course of the bleeding numerous transfusions of whole blood were given, as well as massive doses of Hykinone. Massive hemorrhages continued, however, and the patient expired on the thirty-first hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR DANIEL S. ELLIS: So far as I can tell it is perfectly logical to explain the symptoms up to the time of operation on the basis of cholecystitis and cholelithiasis, and I seriously doubt whether the patient had ever had an ulcer. It seems to me that the decision to operate was made rather suddenly, and from the history I cannot quite figure out why, unless gallstones were visible in the films that were taken.

DR STANLEY M. WYMAN: The x-ray examination was done with the tube in position, and the film shows the hiatus hernia described. The stomach shows no gross defect. On this single film the duodenal cap extends rather posteriorly. It appears a little smaller than usual, but these spot films of the duodenum show no definite constant deformity or crater. I do not see the gallstone that Dr Ellis is interested in on any of these films.

DR ELLIS: As usual, the x-ray films do not tell all I should like to know. The problem, as I see it, is what caused the bleeding. Obviously, the patient died of hemorrhage and cholemia, and it is up to me to explain why he was jaundiced, presumably after the stone had been removed from the common duct, and why he bled enough to cause death. It is mentioned in the early part of the history that the patient had nausea, vomiting and pain. It does not tell how much alcohol he drank. Many patients with cirrhosis of the liver bleed considerably at the time of operation. We do not get any help from the laboratory reports in making the diagnosis of cirrhosis of the liver, other than the fact that the prothrombin time apparently continued to be moderately elevated in the presence,



of massive doses of Hykinone and multiple transfusions. That leads me to believe that some process in the liver caused a failure of prothrombin synthesis and therefore resulted in inability of the blood to clot. Whether this condition in the liver existed at the time of operation or whether it developed following operation is one of the questions to which I should like to know the answer. There can be little doubt that the patient had cholecystitis and cholangitis. The attacks of pain and nausea and vomiting were associated with chills and fever. The description of the liver at the time of operation is that it was slightly small but otherwise normal. We do not have the advantage of knowing about a biopsy report or bromsulfalein test previous to operation. For the moment, I shall say that this patient had cirrhosis of the liver, which would account for the excessive bleeding following operation.

Another condition that might be considered the source of bleeding is purpura, but I can do no more than mention it as a possibility. I can find nothing in the history or in the evidence as given to prove such a diagnosis.

Amyloidosis might give rise to such bleeding but does not explain the preoperative course. We have recently had a patient who bled considerably after operation and who was later found to have amyloidosis. I certainly cannot make such a diagnosis on the basis of the information given.

Recently, there has been considerable discussion in some circles about citrate poisoning and the inability of a damaged liver to handle large amounts of citrate such as this patient might have had in repeated transfusions. I can find no material in the literature, however, that really backs up the fact that citrate poisoning can occur from faulty metabolism of the citrate breakdown to produce an increased bleeding time. I do not know how many transfusions this patient had before operation, the statement is made that he had many afterward — these, of course, were given after he started to bleed.

Was the blood from the rectum bright red or did the patient pass tarry fecal material?

DR. TRACY B. MALLORY: The record is not available, but perhaps Dr. Richardson can tell you.

DR. WYMAN RICHARDSON: The patient passed a considerable amount of obvious blood, not bright red but exactly what one would expect from gastrointestinal bleeding, that was late in the course of the disease.

DR. ELLIS: The statement was made at the time of admission that there had been no bleeding, which was first mentioned shortly before death. If this man had acute portal thrombosis he could have had bleeding into the gastrointestinal tract. This could have been due to portal back pressure or infarction of the bowel caused by retrograde thrombosis of the mesenteric veins. If he had an acute portal thrombosis, he may have had infarction of the liver, with subsequent jaundice. At least

half the cases of portal-vein thrombosis are associated with portal cirrhosis. A large number of them are due to malignant lesions in the porta hepatis. Inflammatory conditions in adjacent areas, such as cholangitis, pancreatitis and subphrenic abscess, also cause portal thrombosis. In this case something was going on under the diaphragm, for when the head of the bed was lowered the patient had pain, radiating to the shoulder — a diaphragmatic pleurisy. Whether he had a frank abscess or a collection of blood without infection, I do not know. I rather think that he had bile in the peritoneal cavity, in addition to the blood, and that the combination of the two was sufficient to cause irritation and symptoms.

From the surgical point of view I wonder why the catheter did not drain immediately after operation. I should like to believe that the liver was not manufacturing bile. On the other hand, the record mentions previous drainage through the cigarette wick and rubber drain in the abdomen, therefore, I take it that bile was leaking around the catheter. This obstruction, then, was most certainly of a mechanical nature. In view of the subsequent events it may well have been due to a blood clot. From the operative notes given it seems that thorough exploration of the common and cystic ducts had been done, and I trust the surgeon who did it. I shall therefore assume that no stones were left and that plugging of the catheter was due to a blood clot coming out of the common duct.

In summary, it seems to me that this patient died of hemorrhage and cholemia, secondary to some process in the liver. He may have had cirrhosis in addition to the cholecystitis and cholelithiasis, but I cannot do more than guess at that. I believe that the portal thrombosis after operation probably explains the subsequent events. I shall therefore say that the portal thrombosis was due to infection and cholangitis, as well as to a peritoneal inflammatory reaction caused by the presence of bile and blood in the peritoneal cavity and around the bed of the drainage.

DR. RICHARDSON: I saw the patient about three days before he died. Unfortunately, the record is not here to keep me honest, but I hope I quote myself correctly. I was asked to explain the bleeding. At that time it became somewhat apparent to me — I do not know whether it was the appearance of the man or something the family said — that he had drunk a great deal of alcohol. How much I do not know, but I should think entirely too much — that is, he drank more than would be good for you and me. I could not determine any reason for the bleeding that was compatible with the normal bleeding and clotting times. My opinion was that he had a severe hepatitis. Dr. Ellis said that cirrhotic patients bleed postoperatively, I wish he would tell me why.

DR ELLIS For two reasons — first, because the ability of the liver to form prothrombin is damaged

DR RICHARDSON This patient's prothrombin time was 23 seconds, against a normal of 19 seconds. That is not enough

DR ELLIS As a matter of fact it was 23 seconds with a control of 15 seconds, which is a little more than I should consider normal in the presence of Hynnone and transfusions, if he did not have some damage to the liver

DR RICHARDSON That level would not account for the bleeding necessarily

DR ELLIS The other reason for the hemorrhage in these cases is the increased vascularity

DR RICHARDSON It may be all right if a diseased liver is involved. That is why this patient bled — lack of fibrinogen or something that we do not know about.

DR ELLIS And also the lack of ability to form prothrombin

DR LEWIS K DAHL The patient would not have bled with this level of prothrombin

DR RICHARDSON I do not believe that the citrate theory fits this case. Diseased livers are apt to bleed, and all the tests of clotting are quite normal or sufficiently near normal not to be the cause of bleeding. I thought that this patient had hepatitis and that the surgeon had removed the gall bladder, being quite confident that this was largely a question of gallstones

#### CLINICAL DIAGNOSES

Acute hepatitis

Massive intraperitoneal and gastrointestinal hemorrhage

#### DR ELLIS'S DIAGNOSES

Acute portal thrombosis

Cholangitis

Cholemia

Massive intraperitoneal and gastrointestinal hemorrhage

#### ANATOMICAL DIAGNOSES

Intrahepatic cholangitis

Massive intraperitoneal and gastrointestinal hemorrhage

Gas-bacillus infection, terminal

Operation cholecystectomy or cholelithiasis, recent.

#### PATHOLOGICAL DISCUSSION

DR MALLORY I am not going to explain the hemorrhage any better than the clinicians have been able to do it. The liver was considerably diseased — it seemed to consist of a bag full of jelly. When touched, it quivered all over. This jelly-like substance was full of bubbles of gas developing so fast that although the bubbles could barely be seen at the beginning of the post-mortem examination, two hours later they were grossly visible. There was therefore a terminal massive gas-bacillus infection that could not have existed very long. Unfortunately, it had a marked destructive effect on the liver tissue, which again made it difficult to know what was going on before death. There was enough left, I believe, to say that this picture was definitely different from the preceding one (Case 33361). In this case the tissues of the portal areas, especially around the bile duct were massively infiltrated with polymorphonuclear leukocytes — not mononuclear cells such as one sees in infectious hepatitis. The picture was that of severe intrahepatic cholangitis. How much damage of liver cells there may have been as well, I am unable to say because of the presence of the gas-bacillus infection. The region of the common duct was carefully explored. No large vessels were found that could have served as a source of massive hemorrhage. The entire intestinal tract, from stomach to rectum, was filled with fresh blood. There were clots of blood in the gall-bladder bed. This was nearly two weeks after operation, and the blood should have been entirely dried up by that time. There was about 2500 cc. of fresh blood in the peritoneal cavity. We could not make out any definite bile staining in the peritoneal fluid.

Nothing else of importance was found.

DR ELLIS I should like to ask why operation was performed on the fifth day.

DR RICHARDSON I only saw the patient just before he died, but I know that the preoperative diagnoses were cholecystitis and cholelithiasis. He was operated on as a routine gall-bladder case.

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## FASHIONS IN MEDICAL WRITING

JUST as practice in the care of patients and in matters of medication and therapy change from decade to decade, so also change the customs employed in the presentation of physicians' thoughts to professional colleagues in the form of medical literature

In the past seventy years there has been a trend in the American medical literature toward more objective factual documentation. All will agree that this has been a step forward, producing clinical articles that are based on tabulation and the case protocols of specifically identified patients rather than on vague impressions. In part, this change has sprung from the tendency of more medical investigators to receive training in fundamental scientific research. One need only look at a few of the articles, in some of the highly specialized journals to

realize that scientific material of the utmost importance is often presented in an article of one or two pages, with an accompanying table or chart. Unfortunately, however, colorful English and in triguing descriptions of clinical events have been carried away in this scientific tidal wave. Our ancestors often wrote clinical articles containing vivid language, which gave the reader a graphic and lasting picture of the clinical situation the writer had in mind, this was good teaching as well as good writing. Much of this skill has been lost, and its loss has been an aspect of the scientific trend one cannot paint a blueprint in lurid colors, and the style of Macaulay is out of place in a series of case reports. Possibly, this trend has gone too far in American medical literature. Some of the English writers at the present time — for example, Ogilvie and Gordon-Taylor — can report clinical material in a way that brings color, interest and humor to the cases.

Two other abuses that are becoming epidemic cannot be dealt with so gently. One of these is the use of what might be called the "secretarial bibliography." Certain medical authors make a specialty of this procedure. The usual practice is to write an article on some rather commonplace subject and to append thereto a bibliography of two or three hundred references.

Just what should be the significance of the bibliography in a clinical article? Is it supposed to be an encyclopedic mention of everyone who has ever thought about the subject before? Or should it represent the background of the writers themselves, who believe that the reader may use the material to his profit and edification? The latter seems to be the more reasonable choice. If one wishes to publish a review article, a long list of references is appropriate, and each bibliographic item is dealt with in detail and its contribution summarized or criticized. The insertion of half a dozen bibliographic references in the middle of a sentence — often after a single word or phrase — simply to indicate that six articles can be found in the *Quarterly Cumulative Index Medicus* leaves the reader with the conviction that the writers never read through this long bibliography before starting their work. It is common knowledge that such extensive bibliographies are often worked up by secretarial

help, this is a prostitution of the medical library and adds nothing to the medical literature. If an author wishes to include a long bibliography and does not wish to write a review article, he should not forget the usefulness of the annotated bibliography, in which a long series of bibliographic references may be mentioned and the contents briefly described so that the reader can pick and choose matters that concern him.

Another modern abuse of medical writing, even more a product of the machine age than the secretarial bibliography, is the "punch-card article" on clinical material. When anthropometric data or the distribution of age, weight and height among school children is being dealt with, the use of a punch-card system may yield material of much interest and information. When, however, a punch-card statistical device is applied to clinical material that has an extremely variable background, the data that come from the machine may have little or no meaning. The old platitude that a chain is as strong as its weakest link might be paraphrased to state that statistical information on clinical patients is of as great value as the thought that has gone into its selection. Merely to analyze a large series of tumors according to whether the patient had red hair or dark hair, large ears or small ears and did or did not smoke cigarettes adds little to knowledge, even though it yields numbers that have two significant decimal places and adapt themselves well to the drawing up of innumerable charts and graphs. As the anthropologist approaches a statistical problem, for example, measurements of head size, he puts in his punch-card system all the standard measurements of the skull that can be reproduced, these are his variables. He then uses the machine as a device for singling out which of these variables are significant in relation to racial grouping. A sick human being, however, demonstrates so many thousands of variables that it is difficult to determine which ones to study on the statistical machine. The result is that the writer or investigator puts into the machine variables that he considered significant at the outset of his investigation. The machine can then only show whether the investigator was right or wrong; it can only reflect what was going on in his mind—it can uncover no new material.

As the punch-card system becomes better known to clinical investigators it will be used more widely, with an increasing flow of articles in which the frequency of variables in the patient's constitution, diet, habit, blood chemical findings and so forth in a certain disease are analyzed. In the preparation of such an article it is always well to put each variable to the following test: "Is this a factor of established importance in the disease—one that has been known for years to affect its incidence, occurrence or outcome?" If the answer to this question is "Yes," the machine has contributed little to knowledge except for affixing the stamp of statistical approval to a previous clinical impression. If, however, the variable analyzed was previously unknown as being significantly related to the occurrence, course or mortality of the disease, this statistical device will teach the reader something of worth.

As one contemplates the volcano of medical literature erupting from the universities, clinics and laboratories of this country, one cannot but express the hope that clinical articles will be written with imagination and color, that they will give a graphic and frank picture of the problems of disease or therapy, the bad shown with the good and the poor results with the cures, and that material relating to laboratory investigations of a fundamental nature will be presented with the utmost simplicity and a minimum of confusing data, without apology or pipe-dream exploration of the future. And lastly, it is hoped that the secretarial bibliography and punch-card article will be used sparingly and to good purpose rather than as a method of showing off the thoroughness of the author's investigative devices.

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## HEALTH CENTERS

THE first health center in the United States, according to an analysis prepared for the Council on Medical Service of the American Medical Association by Dr. Dean F. Smiley,\* was established in Philadelphia in 1912 as a child-health center. There are now at least one hundred and fifty in operation, of various types, under public or private auspices. Many of these are more than health centers con-

\*Smiley, D. F. Health centers under Hospital Construction Act. *J. A. M. A.* 134:1179-1181, 1947.

cerned chiefly with health promotion, they have had added to them welfare, recreational, hospital-service and medical-service functions

A particular and urgent interest in the health center has been necessitated at this time by the passage of the Hospital Survey and Construction Act of 1946. If health centers are to be provided, it is well to know the best types to put into operation under the given circumstances

The most important needs to be met, Dr Smiley believes, are, in order of urgency, as follows: community hospitals of fifty or more beds for rural communities of 20,000 or over, community clinics of ten or more beds for rural communities of 4000 to 18,000, public-health centers to serve as headquarters for single county or multicounty public-health units, and public-health centers to serve as extensions of the single county or multicounty public-health units into the smaller communities

Dr Smiley's chief recommendations are four-fold

That only five functions (communicable-disease control, sanitation, maternal-infant-child hygiene, vital statistics and health education) be generally included under the title of public-health center as that title is used in the Hospital Survey and Construction Act of 1946

That public-health centers be established as needed and as close as is practicable to hospitals in base, intermediate, and rural areas, and that they be integral parts of base medical centers, district medical centers and community medical centers. At every level, however, the public-health center should be administratively independent of the hospital

That, in rural communities of 4000 to 18,000 in need of sick beds but not large enough to afford a fifty-bed general hospital, "community clinics" of ten to forty beds be provided by hospital authorities rather than "public-health and medical-service centers" by public-health authorities

That, in those rural communities where bed service is available in neighboring community hospitals and the urgent need is for public-health and diagnostic facilities, facilities be provided by the public-health center not only for the traditional six-point public-health service but also for

clinical laboratory service and limited x-ray service. Offices should also be included, if desired, for the part-time use of the practicing physician of the community

## MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided

### DEATHS

**CUTLER** — Elliott C. Cutler, M.D., of Brookline, died on August 16. He was in his sixtieth year.

Dr. Cutler received his degree from Harvard Medical School in 1913. He served in World War I with the Harvard Medical Unit and the United States Army Medical Corps. In World War II, as head of the Medical Aid Division of the Massachusetts Committee on Public Safety, he organized a system that served as a model for the rest of the country; later, he was chief consultant in surgery, European Theater of Operations, with the rank of brigadier general. He was Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief, Peter Bent Brigham Hospital. He was a member of the American Surgical Association, Society of Clinical Surgery, New England Surgical Society, American Association for Thoracic Surgery, American Society for Clinical Investigation and American Society for Experimental Pathology, a diplomate of the American Board of Surgery and a fellow of the American College of Surgeons and the American Medical Association.

His widow, four sons and four brothers survive.

**HOWE** — W. Lewis Howe, M.D., of Everett, died on August 18. He was in his seventy-third year.

Dr. Howe received his degree from Tufts College Medical School in 1900. He had practiced medicine in Everett for forty-five years and was for many years a member of the School Committee and Board of Health.

His widow and three sisters survive.

**WISE** — John M. Wise, M.D., of Watertown, died on August 8. He was in his seventy-first year.

Dr. Wise received his degree from University of Buffalo School of Medicine in 1907. He was formerly senior physician at the Middlesex County Sanatorium and was a fellow of the American Medical Association.

His widow and a son survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### PUBLIC-HEALTH CONFERENCE

The Massachusetts Public-Health Conference will be held at the University of Massachusetts in Amherst on September 11 and 12.

The conference, sponsored by the Massachusetts Public Health Association, the University of Massachusetts and the Massachusetts Department of Public Health, is intended to stimulate interest in extending protective health services to communities that lack facilities and personnel. Health officers, milk inspectors, sanitarians, nurses, physicians,

health educators and other health workers throughout the Commonwealth are expected to attend.

Among the topics to be discussed are the following: "Bringing Health Services to Your Back Door," by Dr Haven Emerson, chairman, Committee on Local Health Units, American Public Health Association, "Functions of Health Centers," by Dr Charles F Wilensky, president of the Massachusetts Public Health Association, "Unmet Needs for Children," by Dr Lendon Snedeker, executive secretary of the Massachusetts Study of Child Health Services, "The Importance of Local Health Departments to the Nation," by Dr Herman G Hilleboe, former assistant surgeon general of the United States Public Health Service and recently appointed by Governor Dewey as Commissioner of the New York State Department of Health, and "Dollars for Health," by Dr Vlado A Getting, commissioner of the Massachusetts Department of Public Health. Special section meetings will be held for health officers, health agents, nurses and sanitarians. Governor Robert F Bradford will deliver the keynote address, "Health for Massachusetts," at the opening of the conference.

All those who are interested are invited to attend the two-day conference. Reservations for overnight accommodations may be made by writing to Professor Ralph L France, Marshall Hall, University of Massachusetts, Amherst, Massachusetts.

## MISCELLANY

### RADIO BROADCASTS

"The Medical Center of the Air" is continuing its series of weekly radio broadcasts every Saturday morning from 11:30 to 12:00 (EDT) over station WNAC and the Yankee Network. The programs are sponsored by the Massachusetts Memorial, Beth Israel Boston City and Peter Bent Brigham hospitals which rotate in presenting programs of medical educational interest. Specific diseases and topics of general interest are discussed. The programs are presented as a public service feature without commercial advertising.

## NOTE

Dr Herbert H. Howard, of 270 Commonwealth Avenue Boston, consultant in urology at the Boston City Hospital, was recently installed as president of the American Urological Association.

## CORRESPONDENCE

### SCIENTIFIC EXHIBITS AT ANNUAL MEETING

To the Editor: Each year the Massachusetts Medical Society convenes not only to elect officers but also to stimulate and inform its members by means of papers and exhibits on recent medical progress. An opportunity is also given to commercial houses to exhibit their wares. This year the commercial exhibitors outdid themselves taking up the entire floor of both the ballroom and the foyer. The scientific exhibits, numbering four, were given no prominence whatsoever in the initial arrangements. Two were placed at the rear of a small blind pocket labeled "Ladies' Parlor" off the foyer. One was placed in the balcony and the fourth the Lahey Exhibit, in a corridor leading from the registration desk. Eventually the Vincent Memorial Laboratory Exhibit came to rest opposite the Lahey Exhibit. If one entered the ballroom by the main entrance, this corridor might not have been noticed at all.

One might seriously ask whether the Committee on Arrangements tried to discourage clinicians and research

laboratories from exhibiting. Certainly it is a major reflection on the Society that only four technical exhibits were entered this year, a considerable reduction from last year. The exclusion of these exhibits from the ball room or foyer floor, and their random placement in a corridor a ladies' parlor and a balcony contributed nothing toward encouraging further exhibitors for another year. These exhibits take much time to prepare. That they appear to have been completely ignored in deference to space allotment for commercial firms forces one to conclude that the time taken in their preparation was out of all proportion to the value accredited them by the Committee on Arrangements.

The outlook for next year would be improved by an emphatic statement by this committee that due prominence and consideration would be given the scientific exhibits in planning for 1948.

JOE V MEIGS, M.D.  
Chief Vincent Memorial Hospital

Massachusetts General Hospital  
Boston 14

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Dr Meigs's letter was referred to Dr George G Bailey, chairman of the Committee on Arrangements for 1947-1948. His reply is as follows:

To the Editor: Thank you for calling attention to Dr Joe V Meigs's letter regarding the scientific exhibits at the last annual meeting of the Massachusetts Medical Society. The Committee on Arrangements sincerely regrets that Dr Meigs was dissatisfied with the scarcity and location of the scientific exhibits.

At a recent meeting of the committee the entire subject of exhibits was discussed. It was decided that, as a working basis for next year, ten booths would be assigned for scientific exhibits and that the remainder would be available for commercial exhibits. It may seem that this is a relatively small number to be assigned for scientific exhibits but it is a fact that in the past few years it has been difficult to persuade hospitals and physicians to prepare exhibits for display at the annual meeting. It was further agreed that an effort would be made to solicit exhibits from leading hospitals and clinics as well as from individual clinicians for the meeting. Also a more central location will be assigned to the scientific exhibits. The committee would appreciate hearing from any hospitals or individuals interested in arranging an exhibit for next year's meeting. It would be most helpful if definite plans of any prospective exhibitor could be in the hands of the committee by November 1.

GEORGE G BAILEY M.D.  
Chairman Committee on Arrangements

412 Beacon Street  
Boston 15

## BOOK REVIEWS

*Health Insurance in the United States*. By Nathan Sinai, Dr P.H. Odin W Anderson and Melvin L. Dollar. Studies of the Committee on Medicine and the Changing Order. New York Academy of Medicine. 8" cloth 115 pp. New York: The Commonwealth Fund 1946. \$1.50.

This survey is confined to voluntary medical insurance because compulsory medical insurance, except workmen's compensation in a small way has not yet been established in the United States. The history of the health-insurance movement is covered for the period from 1910 to the beginning of World War II. The various group plans, such as Blue Cross medical society industrial and labor union insurance, federal co-operatives and commercial accident and health insurance are briefly discussed. The attitudes and objectives of the various medical societies including the American Medical Association, the federal departments represented by the Public Health Service and the Social Security Board, labor public enterprise and the general public are fully analyzed and enabling legislation for voluntary plans since 1900 is reviewed. It is stated that the enrollment in nonprofit hospital-service groups increased from 2000 in 1933 to 20,000,000 in eighty seven plans in 1946.

A cumulative summary of hospital and medical acts by states shows that one state, New York had enabling legislation — a hospital act — in 1934 and that a total of thirty five states had hospital acts and twenty five had medical acts in 1945. The greatest increase in legislation took place in 1939 when fourteen states passed hospital acts and six

states medical acts In 1945 there was renewed activity when eleven states passed medical acts, and two states hospital acts Twenty-five of the thirty-five states have both hospital and medical acts Massachusetts passed a hospital act in 1936 and a medical act in 1941

The survey concludes with a review of the characteristic features of voluntary plans and a discussion of the problems presented by such plans, as well as the present status of the health-insurance movement. This monograph should be in all medical and public libraries

*Psychiatric Interviews with Children* Edited by Helen L. Witmer 8°, cloth, 443 pp New York The Commonwealth Fund, 1946 \$4 50

This book is well written and well published The text is divided into three parts In an introduction the author gives a concise and clear account of the nature of child guidance, its history and the purpose and peculiarities of this type of social psychiatry, in which physician and social workers form a perfect team and the patient is considered a part of the family rather than an isolated subject The brief remarks about psychoneuroses and social implications are sound and up to date, utilizing the newest development of psychodynamic psychiatry without loading the text with psychoanalytic terms that may be not acceptable to everyone The main part of the book consists of the presentation of ten actual cases studied by a number of therapists, either psychiatrists or psychologists The clear discussion and presentation of the various interviews with the reactions of the patient and the comments of the therapist give an accurate insight into the proceedings, interpretations and therapeutic dynamics This volume is valuable because it limits theory to a minimum and presents the actual course of interviews—a procedure that any student of psychiatry has rarely an opportunity to follow except with his own cases

*Myasthenia Gravis* By Dr Adalberto R. Goni Translated by Georgianna Simmons Gittinger 8°, cloth, 112 pp, with 10 illustrations Baltimore Williams and Wilkins Company, 1946 Free.

This book, when published in Portuguese, was the first monograph on the subject of myasthenia gravis to appear in over twenty-five years It thus received a warm welcome, and an English translation was much desired by neurologists and others working in the field The author has had considerable practical experience and is fully acquainted with the current literature up to 1943 Thirteen case histories of typical examples of myasthenia gravis are presented

*The Modern Treatment of Diabetes Mellitus Including practical procedures and precautionary measures* By Williams S. Collens, M.D., and Louis C. Boas, M.D. 8°, cloth, 514 pp, with 195 illustrations Springfield, Illinois Charles C. Thomas, 1946 \$8 50

In this excellent treatise on the management of diabetes and its complications, the authors discuss the practical aspects of the subject in an authoritative fashion Except for the first chapter, which gives a historical account of diabetes and the discovery of insulin, there is relatively little in the book regarding the incidence, etiologic factors, pathologic physiology and pathology of diabetes, as stated in the opening paragraph of the volume.

It is refreshing to note that the authors obviously believe in the careful control of diabetes Their sensible recommendations concerning treatment should help to counteract the teaching heard so much in recent years regarding the supposed harmlessness of hyperglycemia and glycosuria

The critical reader with a special interest in diabetes will find various points with which he may not agree. On Page 48 the fasting blood sugar is mentioned prominently as a diagnostic step, and it is implied that if this determination is normal, one should proceed to a formal glucose-tolerance test. To the reviewer, this is too frequent a tendency. Physicians generally should make more use of urine and blood sugar tests done approximately an hour after a meal as a diagnostic step. Often, one may thereby avoid subjecting a patient needlessly to a glucose-tolerance test. Collens and Boas discuss the Exton-Rose test without critical comment, whereas it is fair to state that, with greater usage, it has

lost rather than gained in favor with many clinicians. On Page 52 it is observed that fructose produces a characteristic osazone with phenylhydrazine. The fact is that fructosazone is indistinguishable from glucosazone and that methyl-phenylhydrazine must be used for differentiation

The treatment of the individual case is discussed under eight headings, with a chapter devoted to each, as follows: the obese patient with mild diabetes, the patient of normal weight with mild diabetes, the undernourished patient with mild diabetes, moderately severe diabetes, severe diabetes without ketosis, severe diabetes with ketonuria without acidosis and with ketosis (compensated acidosis), diabetes with clinical acidosis, and the diabetic patient in coma. This makes for a logical, orderly presentation of material but tends to burden the reader with detail and makes treatment seem unduly complicated

In Chapter XIII, the authors recommend glucose intravenously in the treatment of diabetic coma, its use in the first few hours of treatment is considered undesirable and even harmful by certain clinicians. The doses of insulin recommended (page 205) are relatively small, and many would consider them incapable of achieving maximal success

From the discussion of hepatomegaly in juvenile diabetes (page 246) it might be inferred that the enlargement of the liver seen in the untreated or poorly treated patient is due chiefly to lack of choline or lipocaic or related substances. Actually, in human patients, hepatomegaly is almost invariably abolished when the diabetic condition is brought under control with protamine-zinc insulin without the aid of special lipotropic preparations

The book is well printed on good paper and is easy to read. Illustrations, some of which are in color, contribute greatly to the value and appearance of the volume. In the fly on the front cover is included a "Collens Diet Calculator"

*Diabetes A concise presentation* By Henry J. John, M.D. 8°, cloth, 300 pp, with 74 charts and 44 tables St. Louis C. V. Mosby Company, 1946 \$3 25

This volume represents the honest and serious attempt of a clinician with a wide experience in diabetes to set forth in concise form the principles of diagnosis and treatment that he has found useful. A good deal of the material has appeared previously in articles published in medical journals, chiefly between 1929 and 1935. Consequently, the monograph is limited almost entirely to the views of the author and in some respects lacks freshness, breadth and scope of presentation.

The author is to be commended on his interest in the prevention of diabetes. He reasons that if a temporary or prediabetic state can be treated successfully in experimental animals (as in the early stages of diabetes following the injection of anterior pituitary extract), it is conceivable that the same situation may apply in human beings. Despite the inadequacy of present knowledge, the approach of the author is sound and forward-looking

Dr. John, having had much experience with glucose-tolerance tests and their interpretation, devotes considerable space to this subject. Although there will not be general agreement regarding diagnostic standards, his recommendations are fair and safe

The author believes that infection must be assigned a causative role in the etiology of diabetes in children. This point is debatable, and there is much evidence to the contrary. Acute infections are frequent in early life, and yet diabetes only rarely has its onset in childhood. Dr. John is one of the pioneers in the establishment of summer camps for diabetic children and writes instructively of this matter

In a chapter on pregnancy and diabetes much space is taken up with a discussion of the diagnosis of melituria in pregnancy, and little attention is given to the all-important problem of obtaining live babies. No mention is made of the recent phenomenal success attained by the careful and continuous observation of diabetic women during pregnancy and their treatment with large doses of estrogen and progesterone

One chapter is composed of brief paragraphs presenting some "do's" and "don't's." The advice given is practical and sensible

This small volume contains a great deal of practical information and can be read with profit by practitioners and those with a special interest in diabetes. It cannot be con-

considered a complete monograph on the subject. It is unfortunate that, presumably owing to shortages, an inferior paper was used in the printing.

**Adolescent Sterility.** A study in the comparative physiology of the infundibility of the adolescent organism in mammals and man. By M. F. Ashley Montague. 8 cloth 148 pp with 33 tables. Springfield Illinois Charles C Thomas, 1946 \$3.50

The question that the author considers is What, if any interval of time normally elapses between the appearance of the first menstruation, the menarche and the ability to conceive and carry a fetus to term? It is pointed out that the first observers to draw attention to the phenomenon of the infertility of adolescent human females were ethnologists working with tribes in Melanesia New Guinea South Africa the Philippines and other areas. In such simple societies the infertility could not be explained by contraception, early sexual life or free mixing of lovers. The author then presents evidence for the presence of adolescent sterility in lower mammals, such as the mouse and the cow. In the Rhesus monkey the adolescent period is marked by the slow development of two primary phases of that of puberty which begins with the menarche, and that of nubility the period at which the female becomes capable of procreation. The work of Allen, Hartman and Corner had already shown that the early menstruation of the female Rhesus monkey is normally incapable of ovulation. The chimpanzee a close relative of man, is in most cases normally incapable of conceiving until some appreciable time from the establishment of the menarche. In a chapter on adolescent sterility in man the author gives many tables of the menarche-conception interval. The adolescent sterility in the human female is up to the age of about twenty three years.

The book is written in readable style and has an excellent bibliography. Physicians students of growth physiologists, psychologists anthropologists and educators will find this volume worthy of careful study.

**Urgent Surgery.** Edited by Julius L. Spivack M.D. Volume I. 8<sup>th</sup> cloth, 714 pp with 244 illustrations. Springfield, Illinois: Charles C Thomas 1946 \$10.00.

The editor points out in the preface that the scope of emergency surgery has been greatly widened within recent years. Today, competent surgeons working with adequate facilities are available in many rural communities that were formerly without such services, and the problem has changed from what must be done in a few minutes to what should be done within a few hours or days. For this reason the editor has chosen the title "Urgent Surgery" for this book rather than the more frequently used term "Emergency Surgery".

The eighteen chapters have been written by eight surgeons some of them specialists outside this country. Twelve chapters were written by the editor and another was revised by him. The first five chapters, which deal with transfusion infusion shock anesthesia and laparotomy incisions are in general well written, reflecting the considerable experience of the authors. It seemed to the reviewer that in many places greater use could have been made of the many valuable lessons learned from the military surgery of the recent war, such as the use of blood over plasma in the treatment of shock, the use of blood in the treatment of extensive burns, the advantages of Pentothal over Evipal Sodium, the usefulness of a median or paramedian incision rather than a transverse incision when the extent of the intra abdominal disease is unknown and the treatment of perforating wounds of the rectum.

The chapter on the liver and bile ducts by Dr. Pnbram is particularly comprehensive. Many surgeons might disagree with his emphasis on the value of electrocoagulation of the gall bladder, but in all probability in his hands at least, it affords a satisfactory way of dealing with the acutely inflamed gall bladder. The chapter is long but interesting throughout and would well repay reading by anyone interested in the surgery of the liver or biliary tract. Dr. Warren Cole has written an excellent chapter on the urgent surgery of the pancreas, and as is found throughout the book, many surgical problems are considered that are ordinarily not included in works on emergency surgery.

A thorough review of the problem of intestinal obstruction by Dr. John R. Paine if carefully read, should help to correct some of the misuse of the nonoperative treatment of intestinal obstruction. The chapters on stomach surgery congenital stenosis of the pylorus, appendicitis and urgent intestinal surgery in infants written by the editor, are extremely good and together with those previously mentioned and others, form a volume on urgent surgery that is both practical and comprehensive. There is an extensive bibliography at the end of each chapter and the book is well illustrated.

**Diagnosis and Treatment of Menstrual Disorders and Sterility.** By Charles Mazer, M.D., and S. Leon Israel M.D. Second edition, revised and enlarged. 8<sup>th</sup> cloth, 570 pp, with 133 illustrations. New York Paul B. Hoeber, Incorporated 1946 \$7.50.

The first edition of this book, which was prepared with the family physician in mind, was well received. The second edition, which has been revised extensively and which brings the important subjects of menstrual disorders and sterility up to date, is written to serve as a guide to the general practitioner of medicine and to the medical student. There is much in the book, however, of considerable value to the specialist in gynecology and obstetrics.

The first chapter deals with the pituitary gland, and the second with the ovary. The effect of estrogen on the normal menstrual cycle, on uterine mobility on the fallopian tubes on the vesical sphincter on the anterior hypophysis, on the ovary on the breasts on libido and on the central nervous system as well as the constitutional effects, are discussed. The relative potencies of the several estrogens in terms of rat units are given in table form. The second portion of this chapter deals with the corpus luteum hormone progesterone. Puberty in the female is taken up extensively in the third chapter. The normal menstrual cycle forms the subject matter of another chapter this cycle being divided into the following phases the menstruating or discharging phase the proliferative estrogen or preovulatory phase and the secretory progesterone or postovulatory phase. Each is well described and illustrated and the photomicrographs are well chosen and executed. The hormone balance of the normal menstrual cycle is considered. Abnormal manifestations of the menstrual cycle dysmenorrhea premenstrual tension, menstrual migraine abnormal breast hyperplasia cyclic intermenstrual pain and vicarious menstruation are covered. Twenty-eight pages are devoted to dysmenorrhea this subject is thoroughly elaborated on and the treatment, both surgical and nonsurgical, is considered. Amenorrhea and hypomenorrhea are reviewed and three types of hypomenorrhea are described the normal, the endocrine and the uterine. The treatment of uterine bleeding — of both systemic and organic origin from such lesions as carcinoma of the cervix chorioepithelioma cervical polyps malignant tumors of the ovary pelvic inflammatory disease and endometriosis — is well presented. The phrase "dysfunctional uterine bleeding" describes the menorrhagia or metrorrhagia caused by impairment of the endocrine factors that normally control the menstrual function more accurately than the more frequently employed term "functional uterine bleeding". The treatment of dysfunctional uterine bleeding of puberty the childbearing age and premenopausal and postmenopausal bleeding are stressed.

Nearly a quarter of the book concerns the problem of sterility this condition being discussed under the following headings general considerations the influence of gross pelvic lesions on fertility, the factor of insemination of the cervix the tubal factor in sterility and the endocrine factors in sterility of the female. The male factor in barren marriages and artificial insemination are also mentioned, and the well prepared contribution on the diagnosis and treatment of male sterility by Dr. Charles W. Charny adds to the value of the book.

Chapters on the analysis of 695 cases of primary and secondary sterility and on relative sterility follow. A bibliography containing the important contributions to each subject is appended to each chapter, and an appendix containing the commercially available standardized endocrine products completes the volume.

The second edition of this well written book will prove of value to the specialist as well as to the general practitioner and the medical student.



## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*A Textbook of Pathology*. By E. T. Bell, M.D., professor of pathology, University of Minnesota Medical School. Contributors: B. J. Clawson, M.D., professor of pathology, University of Minnesota Medical School, and J. S. McCartney, M.D., associate professor of pathology, University of Minnesota Medical School. Sixth edition, enlarged and thoroughly revised. 8°, cloth, 910 pp., with 500 illustrations and 4 color plates. Philadelphia: Lea and Febiger, 1947. \$10.00.

This textbook has been designed for the use of students during their clinical training and as a reference source for the practicing physician. The number of editions vouches for the popularity and soundness of the book, which was first published in 1930.

This edition has been revised in the light of current knowledge, and much new material has been added, especially on the vitamin deficiencies and tropical diseases. The number of illustrations has been increased, and a list of carefully chosen references is appended to each chapter. The volume is well published in every way.

*Speech and Human Relations: An approach to the physical and psychological factors involved in effective oral communication*. By Joseph G. Brin, Ph.D., director, Office of Speech Counseling, Boston University. With a foreword by Frederick C. Packard, Jr., associate professor of public speaking, Harvard University. 8°, cloth, 166 pp. Boston: Bruce Humphries, Incorporated, 1946. \$2.50.

Professor Brin has written, in a simple manner, a practical handbook for persons called on to make public addresses. He does not give hard-and-fast rules, but discusses the necessary factors leading to a good speechmaking personality. Chapter twenty-one, consisting of one page, is valuable, since it lists in tabular form the virtues and vices of good speech form. The small volume is well published and should prove useful to persons called on to make public appearances.

*A Textbook of Medicine*. Edited by Russell L. Cecil, M.D., Sc.D., professor of clinical medicine, Cornell University Medical College, consulting physician, New York and Veterans hospitals, and visiting physician, Bellevue Hospital. With the assistance of Walsh McDermott, M.D., associate professor of medicine, Cornell University Medical College, and Harold G. Wolff, M.D., associate professor of neurology, Cornell University Medical College. Seventh edition. 4°, cloth, 1730 pp., with 244 illustrations. Philadelphia: W. B. Saunders Company, 1947. \$10.00.

This standard textbook, first published in 1927 and revised every three or four years, has, despite the limitations of the war years, been brought up to date in this new edition. The work is the joint effort of a hundred and sixty-two American physicians who are acknowledged authorities in their special fields of medicine. Twelve new authors have written sixteen articles on subjects not contained in the previous edition, including deficiencies of vitamins A, E and K, hypervitaminosis, drug allergy, marijuana intoxication, porphyria, acrodynia, narcolepsy, headache, psychosomatic medicine, hemifacial spasm, diphtheritic polyneuritis, the hemoglobinurias and blackwater fever. Because of the death or retirement of a number of authors fifty-three subjects have been rewritten by new authors. All contributions are signed. Selected references are appended to each subject. The work has been kept in one volume by the use of a double-column format and a light paper. The type and printing are good, but if the material is increased in subsequent editions a two-volume setup, using heavier paper, should be seriously considered. The light paper used in this edition will not stand hard usage. The book should prove useful to physicians and is recommended for all medical libraries.

*Diseases of Metabolism: Detailed methods of diagnosis and treatment*. Edited by Garfield G. Duncan, M.D., director, Medical Division, Pennsylvania Hospital, and clinical professor of medicine, Jefferson Medical College, Philadelphia. Second edition. 8°, cloth, 1045 pp., with 167 illustrations. Philadelphia: W. B. Saunders Company, 1947. \$12.00.

This standard text, first published in 1942, has been revised and brought up to date. It is the work of twenty-one recognized authorities in their respective fields. No material has been added, including a discussion of all forms of diabetes. The chapter on nutritional and metabolic aspects of disorders of the blood has been rewritten in the light of the broadening knowledge in this field. The vitamins and known clinical value are dealt with in detail, and folic acid and the *Lactobacillus casei* factor are considered in relation to nutrition and metabolism. The lists of selected references appended to the chapters have been expanded but have not been made comprehensive. The book is well published in every way. It should be in the libraries of clinicians and all medical libraries.

## NOTICES

## NORFOLK DISTRICT MEDICAL SOCIETY

The first 1947-1948 meeting of the Norfolk District Medical Society will be held at 8:00 p.m. on Tuesday, September 23, at the Boston Medical Library, 8 Fenway, Boston, entitled "Boston University Night." The program will consist of five papers of general interest by members of the faculty of Boston University School of Medicine.

## PROGRAM

"Boston University School of Medicine: A brief account of stock." James M. Faulkner, dean and professor of clinical medicine.

"The Clinical Use of Benadryl and Pyribenzamine." Francis C. Lowell, associate professor of medicine, physician, Massachusetts Memorial Hospitals, member, Evans Memorial.

The anti-histamine activity of Benadryl and Pyribenzamine will be discussed, together with the relative merits of these two drugs in the treatment of urticaria, hay fever and other allergic conditions.

"Surgical Management of Carcinoma of the Esophagus and Cardiac End of the Stomach." John W. Stedee, assistant professor of thoracic surgery, visiting surgeon, Massachusetts Memorial Hospitals.

This paper is based on operative experience with approximately 90 cases. It concerns itself particularly with newer developments in diagnosis and surgical care and consequent improvement in end results.

"Folic Acid: Its value and its shortcomings." Joseph F. Ross, associate professor of medicine, physician, Massachusetts Memorial Hospitals, member, Evans Memorial.

Folic acid in oral doses of 1.25 to 15 mg. daily is capable of inducing and maintaining hematologic remissions in patients with pernicious anemia. There is evidence that better blood levels may be maintained with a combination of folic acid by mouth and liver extract by injection than with either medication alone. Folic acid will not prevent the development or progression of subacute combined degeneration in patients with pernicious anemia. Large daily doses actually appear to predispose to subacute combined degeneration, and to cause its progression after liver extract therapy is started. It is possible that large doses of synthetic folic acid may interfere with the metabolism of glutamic acid by the central nervous system.

"Physiological Aspects of Surgery of the Autonomic Nervous System." Reginald H. Smithwick, professor of surgery, surgeon-in-chief, Massachusetts Memorial Hospitals.

Surgery of the autonomic nervous system will be discussed from a physiologic viewpoint, with particular reference to methods of study and the nature of the therapeutic effect.

All physicians and medical students are invited to attend. A collation will be served.

(Notices continued on page xvii)

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## FROSTBITE\*

### Physiology, Pathology and Therapy

KURT LANGE, M.D.,† DAVID WEINER, M.D.,‡ AND LINN J. BOYD, M.D.§

NEW YORK CITY

THE origin of gangrene subsequent to exposure to cold air or contact cooling has found the most diversified explanations. The general trend of opinions seems to have two different directions

seems to believe that injury to muscles and other tissues is subsequent to the damage of nerve fibers, which represents the main feature of the disease. Lewis and Love<sup>2</sup> went so far as to attribute most



FIGURE 1 Photomicrograph (x110) of Tissue from an Untreated Rabbit Two Days after Exposure

Note the interstitial edema and leukocytic infiltration. All vessels are filled with red-cell masses

One group, under the leadership of Blackwood<sup>1</sup> and Ungley and his collaborators,<sup>3</sup> attributes most of the damage to a peripheral vasoneuropathy and

of the damage following frostbite to the bursting of individual cell membranes by the formation of ice crystals. Stimulated by the early studies of Rotnes and Kreyberg,<sup>4</sup> another group, consisting of Greene,<sup>5</sup> Siegmund<sup>6</sup> and Friedman,<sup>7</sup> regards the formation of "thrombi" as the cause of gangrene.

In World War II the casualties due to frostbite were exceedingly numerous. All armies were concerned with this problem, and the number of cases was greatly increased by the severe exposures encountered in high-altitude flying.<sup>8</sup> Damage to the extremities with subsequent gangrene was frequent, and death due to so-called "shock" from

\*From the Department of Medicine, New York Medical College Flower and Fifth Avenue Hospitals and the Research Unit, Metropolitan Hospital.

This study was aided by grants from the John and Mary R. Markle Foundation and by contracts between the Council on Medical Research of the Office of Scientific Research and Development and the Research and Development Board of the Office of the Surgeon General of the United States Army and the New York Medical College.

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laries, forming sludge that contains some platelets but little fibrin. These occlusive red-cell masses are not true fibrin thrombi but should be called "agglutinative thrombi"<sup>12</sup> (Fig 1). \* Three to eight days after exposure these agglutinative thrombi start to undergo hyalinization, resulting in completely hyalinized occlusive masses (Fig 2).

It is interesting to note that, in accordance with the observation of Siegmund,<sup>6</sup> the protein content of all blisters examined while still in the liquid state

since some of the damage to muscles and nerves seems to be due to interstitial fibrin deposition leading to fibrosis, it appeared interesting to determine whether heparinization would interrupt the chain of events.

Twenty-one rabbits, exposed to cold by immersion of one of their hind legs in alcohol at  $-30^{\circ}\text{C}$  for thirty minutes, were heparinized intravenously for five or six days after exposure, the clotting time being kept between 30 and 60 minutes (Lee-White



FIGURE 5 Photomicrograph ( $\times 110$ ) of Tissue from a Heparinized Rabbit Four Days after Exposure  
The blood vessels are empty or filled with normal content

was almost identical with the plasma protein content of the subject. Within twenty-four to forty-eight hours a dense fibrin clot was formed in every blister. It may be assumed that the same process takes place in the interstitial space and thus gives rise to the subsequent fibrosis and collagenous deposition noted in histologic sections, a process described by Rémy and Thérèse<sup>13</sup> as "lardaceous inflammation." Many lymphatic vessels also show clogging with fibrin deposition (Fig 3). All this can be attributed to the tremendously increased capillary permeability.<sup>14</sup>

#### THERAPY

Since the gangrene subsequent to frostbite is due to the occlusive red-cell sludge in the capillaries and

\*We are indebted to Major Nathan B. Friedman at the Army Institute of Pathology, Washington, D. C., for permitting us to use the photomicrographs that resulted from our collaboration.

method). Eighteen of the animals escaped gangrene completely, whereas 3 showed some surface lesions without loss of the limb. Twenty control animals, exposed in the same way but not heparinized, lost their legs by complete gangrene, including the bone. These animals showed dry gangrene with spontaneous self-amputation (Fig 4). Except for sterile dressings no surgical intervention was necessary in any of the animals. These findings, together with experience in 14 human patients with frostbite, treated before the introduction of heparin therapy, convinced us that an extremely conservative approach is indicated so far as amputations are concerned. Self-demarcation and the astounding recuperative power of frostbitten tissue force one to assume an attitude entirely different from that in cases of gangrene due to arteriosclerotic vascular disease.<sup>14</sup> Histologic examinations of the exposed

legs of the heparinized animals reveal that the red-cell conglomerates, regularly found in all smaller vessels of nonheparinized exposed animals, are missing.<sup>12</sup> The vessels are found empty or with a normal content of cells and plasma (Fig 5). Since swelling and increased permeability, as evidenced by fluorescein tests, are observed to the same extent in heparinized as in untreated animals it must be assumed that the increased permeability leads to the accumulation of the red cells by stranding but that they cannot stick together if heparin is present in the blood stream.

A group of 8 volunteers who were undergoing treatment for subacute bacterial endocarditis at the Jewish Hospital of Brooklyn were put at our disposal through the kindness of Dr Leo Loewe.<sup>13</sup> In 4 the frostbite was accomplished by means of a porcelain crucible filled with dry ice and applied without pressure to the skin of the lateral aspect of the upper arm for ten minutes. An area about 2 cm in diameter came in contact with the skin, which attained a temperature of about  $-22^{\circ}\text{C}$ . Heparinization was started immediately after exposure. One volunteer served as a control. The others were subjected to local refrigeration in the same manner but for two exposures of thirty minutes each. The initial or control exposure was permitted to develop for six days before the second frostbite was induced, immediately followed by subcutaneous injection of heparin in Pitkin menstruum.\* The clotting time in the treated cases was kept between 25 and 60 minutes. All adequately treated lesions escaped deeper injuries, whereas the control subjects showed areas of central necrosis approximately 1 cm in diameter and varying from 3 to 5 mm in depth.

A second group, consisting of 4 volunteers (conscientious objectors<sup>†</sup>), was subjected to freezing of an area 3.5 cm in diameter for thirty minutes by means of beakers filled with dry ice. Each volunteer received at least four exposures, including an untreated control, immediate heparinization for six days subsequent to exposure, heparinization for six days after an initial delay of twenty-four hours and heparinization for six days after an initial delay of twenty-four hours during which the exposed part was kept cool by means of an icebag applied to the lesion without pressure, to check on the validity of the concept that cooling subsequent to frostbite improves the course.<sup>14</sup>

The results were similar in all the volunteers. The untreated exposure led to gangrene. Immediate heparinization lasting six days prevented gangrene. Heparinization after a twenty-four-hour delay at room temperature gave almost as good a result as

immediate heparinization. Cooling in the interim produced the poorest results (Fig 6). Blister formation, which takes place rapidly in all exposed areas, is prevented in lesions kept cool after exposure. Immediately after the ice bag has been removed, however, the blisters arise rapidly and are even larger than those in the control lesions. This delay in the appearance of the blister may have led

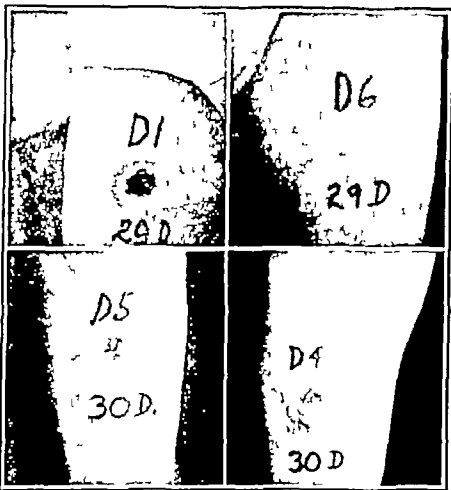


FIGURE 6. Photographs of Skin Lesions on Leg, following Exposure to a Beaker Filled with Dry Ice

The two upper photographs, taken twenty-nine days after exposure, show two lesions in a volunteer, with the first (left) the subject received no treatment, and with the second (right) the subject was heparinized immediately and for six days after exposure. The lower ones, taken thirty days after exposure, show two other lesions in the same volunteer, with the first (left) the subject was heparinized beginning twenty-four hours after exposure for six days, and with the second (right) the subject was treated in the same way except that the area was cooled during the twenty-four hours after exposure.

to the belief that cooling after exposure to low temperatures is beneficial.

The blister content in all heparinized patients stayed liquid throughout. No clot formation was noticed. If the blister did not rupture in the initial phase of marked tension its content was slowly resorbed, a loose shriveled piece of skin remaining on the exposed spot. The fact that heparinization keeps the interstitial fluid, with all its constituents, resorbable is of importance in the prevention of subsequent fibrosis and collagen replacement.

A third group of 3 volunteers (conscientious objectors) was subjected to freezing of an area 5 cm in diameter by means of a metal capsule kept at  $-30^{\circ}\text{C}$ . for thirty minutes. Each volunteer received at least five exposures that subsequently

\*We have abandoned the use of heparin in Pitkin menstruum because of the great pain that accompanies the deposition. In animal experiments large hematomas were noted at the point of the second and subsequent injections that led to exsanguination of the animals. In the animals, doses were used that were just sufficient to keep the clotting time for twenty-four hours between 30 and 60 minutes.

†Made available by Selective Service

received, respectively, no treatment, warming for twenty-four hours after exposure but no heparinization, immediate heparinization for seven days subsequent to exposure, heparinization for seven days after an initial delay of twenty-four hours and heparinization for seven days after an initial delay of twenty-four hours during which the exposed part was warmed by an electric heating pad. The results were similar to those in the previous group. The untreated exposure led to gangrene, warming without heparinization made the gangrene more extensive, immediate heparinization prevented gangrene

It was conspicuous in all the volunteers that the individual reaction to a standard exposure varied widely but was rather constant in the same subject. An exposure that consistently led to extensive gangrene of the entire exposed area in one volunteer failed to produce any tissue breakdown on repeated attempts in another. It may thus be possible to screen persons with an unusually high sensitivity to cold by means of standard test procedures.

The heparinization in the last two groups and in the following cases was carried out by intra

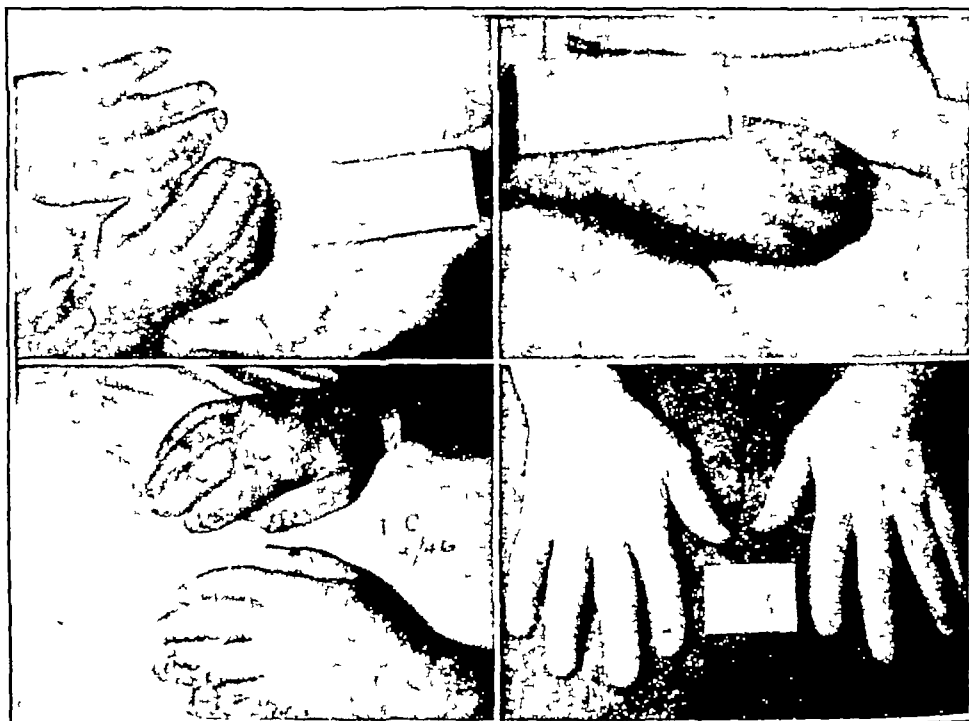


FIGURE 7 Photographs of Hands That Were Exposed to a Temperature of 14 to 18°F for Twelve Hours

The upper left photograph, taken six hours after exposure, shows edema and hemorrhagic blistering. The upper right, taken twenty-four hours after exposure, showed marked edema and large blisters. The lower left, taken four days after exposure and during heparinization, shows considerable edema but there was evidence of good circulation beneath the blisters. The lower right, taken three weeks after exposure, shows a complete return to normal, except for loss of the nails.

completely, and heparinization after twenty-four hours gave almost as good a result as immediate heparinization. Warming in the interval before heparinization produced a lesion that was almost as large as the untreated control lesion, although not so severe as the lesion with interval cooling in the previous group of volunteers. Although loss of tissue was completely prevented in the cases with early heparinization all sensation was lost for at least three months. The same loss of sensation occurred in the treated animals with complete maintenance of tissue. The motor disturbances in these animals, as demonstrated by dragging of the leg, disappeared in four to six weeks.

venous drip. Approximately 300 mg of heparin in 2000 cc of physiologic saline solution per twenty-four hours was given at the rate of approximately 20 to 25 drops per minute. The clotting time (Lee-White method) was kept between 30 and 60 minutes and was checked every twelve hours. No untoward effects were seen in any of the cases treated by this method. Whenever possible, a vein on the middle part of the extensor surface of the forearm was used for the administration of the intravenous drip. The needle and a wide loop of the connecting tubing were fixed to the forearm by adhesive tape. No splint was used at any time, the patient thus being permitted to employ the

arm freely for eating and writing. The patient was even permitted to get off the bed while it was being made. In no case was it necessary to insert the needle more than twice.

Two actual cases of severe frostbite were treated by this method.<sup>17</sup> One patient had been exposed to a temperature of 12 to 13°F for eight hours while lying with bare hands motionless on the pavement. The other had been exposed to a temperature between 14 and 18°F while lying motionless with bare hands on the pavement for twelve hours. Both patients had severe degrees of hemorrhagic blistering within twenty-four hours of exposure. Heparinization was started six and ten hours respectively after the exposures and carried out according to the method mentioned above for seven and five days respectively. The hands were dressed under sterile conditions, since frostbitten tissues seem extremely susceptible to infection. Precautions similar to those employed in the treatment of burns were used, and wet penicillin dressings (1000 units per cubic centimeter) were applied to the blistered and denuded areas. Both patients escaped any loss of tissue except for the loss of the nails (Fig. 7). Although it cannot be stated with certainty that without treatment gangrene would have ensued, there is good reason to assume from previous experience that this would have occurred.

#### SUMMARY

Gangrene subsequent to exposure to subzero temperatures in a dry surrounding (frostbite) was frequent in wartime and is by no means rare in civilian life.

The exposure to cold leads to a marked increase in capillary permeability that produces a rapid loss of plasma with stranding of the red cells in the capillaries. The red cells tend to stick together and to form occlusive masses, which finally undergo hyalinization.

If heparinization is begun within forty-eight hours of exposure and continued for seven to nine days and the occlusive red-cell masses do not form, and subsequent gangrene is thus prevented as shown in animal experiments.

The plasma that leaks into the interstitial space and into blisters forms a dense fibrin deposit.

Heparinization keeps this interstitial fluid liquid and resorbable. Cooling for twenty-four hours after the exposure increases the severity of the lesion.

Warming to 44°C for twenty-four hours after exposure also increases the severity of the lesion. Room temperature seems to be best.

Heparinization of 15 human volunteers exposed to experimental frostbite revealed that gangrene can be prevented by this method. Damage to motor and sensory nerves, however, is not completely avoided.

Sensitivity to cold differs widely between different persons but is rather constant in the same subject. Exclusion of sensitive persons by spot freezing may thus be possible.

Two actual cases of severe exposure to cold that should have led to gangrene were treated by heparinization for five and seven days respectively. Both patients escaped any loss of tissue.

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## ACUTE SUBPECTORAL ABSCESS A SURGICAL EMERGENCY\*

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CASE reports of acute subpectoral abscess and suppurative lymphadenitis — or “subpectoral phlegmon,” as it is sometimes called — have appeared occasionally in both the American<sup>1-3</sup> and the foreign<sup>4, 5</sup> medical literature. The authors usually state that the condition is of relative infrequency, a contention seemingly borne out by a lack of any collected series. A review of the surgical records of the Massachusetts Memorial Hospitals for the past fifteen years reveals a group of 5 cases of acute subpectoral abscess or suppurative lymphadenitis, and 1 case is added from private practice.

Because the nature and behavior of this form of localized suppuration is unfamiliar to many physicians, it is apt to be treated expectantly and conservatively for relatively long periods. Surgery is usually resorted to after the process has spread widely, with extensive tissue destruction, and after a large abscess has broken into the axilla. Unfortunately, during this period the patient has had to endure a painful and toxic course of several days', or even weeks', duration. He may also have run the risk of extension of the suppuration into deeper and more vulnerable regions, such as the subscapular space, the pleural cavities, the mediastinum and the blood stream. Even when these serious complications do not develop he may experience prolonged disability from atrophy of disuse, as well as constricting scar tissue about the shoulder girdle. Surgical drainage is essential, since the sulfonamides and antibiotics cannot be relied on to control this type of infection. The very mechanism by which these agents ameliorate bacterial infection may delay liquefaction of the involved nodes and reduce the local inflammatory signs. As a result it may become more difficult to identify the site of the infection clinically, and the course prior to operative intervention and relief may be prolonged.

The essential pathology in this condition has been described in conjunction with several of the case reports referred to above. Bacteria of high virulence draining through lymphatic vessels from the primary focus, usually a relatively minor infection somewhere in the upper extremity, are filtered out by the infraclavicular lymph nodes. These nodes lie along the courses of the subclavian vessels lateral to the anterior scalenus muscle and the

axillary vessels as far laterally as the axillary fascia and in the adjacent subpectoral adipose tissue. The infected nodes rapidly become swollen and edematous along with the surrounding fat and may proceed to necrosis and frank suppuration within a few days. Kanavel,<sup>6</sup> who presented an excellent description of the condition, called it a “subpectoral phlegmon.” He considered it to be generally secondary to infection of the middle finger. Occasionally, the primary focus is on the chest wall or shoulder area or not even found. The infecting organism (as in 4 of the 6 cases presented below) is usually a streptococcus. Subpectoral infections due to other organisms, such as a staphylococcus (Case 6), are likely to result in a less fulminating pathologic process and a slower development of frank abscess. The infected mass of lymph nodes and the pus produced in association with it are enclosed in a fascial envelope whose lateral wall is formed by the tough axillary fascia. The relatively high pressure developed within this sac by the expanding inflammatory process provides a reasonable explanation for the great pain suffered by the patients. Edema and congestion of the overlying muscles and other soft tissues undoubtedly contribute to the general swelling of the region and to the symptoms. As the abscess enlarges, the axillary fascia may prove a more effective barrier to the suppuration than the less dense fascial planes beneath the scapula, along the vascular channels into the upper arm or toward the mediastinum. Pus may therefore dissect for considerable distances along these pathways before breaking out into the axilla.

The clinical syndrome in acute subpectoral abscess follows a fairly standard pattern. The patient develops pain in the shoulder and subpectoral area that is usually mild in the beginning but later is often exceedingly severe, there is also some malaise and fever. The shoulder becomes lame, and motion is limited and painful. When the infection is streptococcal the patient rapidly becomes extremely toxic, with a high temperature, chills, excruciating pain in the shoulder area and, in some cases, stupor or delirium. Infections due to other organisms, however, are less likely to manifest these more acutely toxic symptoms. Nearly from the beginning, there is a diffuse, although often only slight, swelling in the subpectoral region, the shoulder, the axilla and, to a lesser extent, the supraclavicular fossa; later, these areas may actually bulge. Tenderness may be marked. There is usually some local heat, redness and perhaps cutaneous edema. There

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may be a suggestion of deep induration, particularly beneath the pectoral muscles, but fluctuation usually cannot be elicited. This absence of fluctuation until a late stage of the disease, when a large abscess has broken out into the axilla, has two explanations. Initially, the pathology described above consists of a phlegmonous inflammation of the lymph nodes and surrounding fat, if the patient is seen at that time, of course, no fluctuation can be expected. Secondly, all the tissues involved are enclosed in the tough, resistant envelope of axillary and subpectoral fascia, deep beneath the pectoral muscles. Despite the presence of liquid pus here, fluctuation is difficult to demonstrate, therefore, until the suppuration has broken through the fascia into the subcutaneous fat of the axilla. This may require a week or more. A few small hyperplastic lymph nodes can be felt in the axilla or supraclavicular region but do not impress the examiner as being sufficient to explain the degree of fever and toxicity. The local findings in general suggest an acute inflammatory process in the region of the shoulder, and to those unfamiliar with the syndrome, the actual location of the infection may be puzzling and obscure. The shoulder joint and the neighboring bursas may be under suspicion, particularly since motion in the shoulder joint is limited and painful and the arm is held in some abduction\*.

Early incision and drainage of the subpectoral and intraclavicular spaces provide the treatment for this type of infection and are indicated whether a frank abscess or only edematous masses of lymph nodes, with or without beginning suppuration, are encountered. Pain and toxic symptoms are relieved promptly in either case, and there is usually a dramatic fall in the temperature. Surgical drainage also permits bacteriologic studies and identification of organisms that may be susceptible to sulfonamides and antibiotics.

Most of the patients in this series were treated before modern antibacterial agents came into general use. In only 1 case was an agent theoretically specific for the causative bacteria administered in adequate dosage. Since the symptoms and signs failed to improve after more than forty-eight hours of intensive treatment with penicillin preoperatively but responded dramatically to simple incision and drainage of the subpectoral space, it is almost certain that the process would not have resolved under the medical therapy alone. Little actual pus was encountered in this particular case, the chief finding being a mass of swollen and edematous lymph nodes and fat, culture of which revealed a hemolytic streptococcus. Sulfonamides and antibiotics are probably helpful in limiting the spread of the

infection and should therefore be employed in all cases as adjuncts to the surgical treatment.

The technic of surgical drainage is simple. Direct access to a subpectoral abscess may be obtained by incision of the axillary fascia along its junction with the lateral margin of the pectoralis major muscle followed by breaking through of the abscess wall by blunt dissection. If only a mass of infected lymph nodes is encountered, the forefinger may be used to dissect bluntly well up into the space along the axillary vessels as high as the anterior scalenus muscle. A slightly curved skin incision made at right angles to the anterior axillary fold rather than parallel to it should reduce the post-operative scar disability, an important consideration. When necessary, counterincisions are made to gain good dependent drainage, and several Penrose drains are inserted.

### CASE REPORTS

**CASE 1.** C. M., a 54-year-old man was admitted to the Burbank Hospital, Fitchburg, Massachusetts, on July 14, 1939. Four days previously mild chills and fever, with pain and stiffness at the base of the neck on the left, had developed. These symptoms were interpreted initially as being due to influenza. On the following day the pain became worse, the patient had a high temperature, and a swelling appeared in the left pectoral region.

When the patient was seen by one of us (T. J. A.) in consultation on the day after admission the temperature was 102°F and he appeared extremely toxic and had some difficulty in breathing. The left pectoral region was involved in a massive, tense swelling extending from the clavicle down over the midportion of the chest and also into the axilla. The overlying skin was cyanotic and showed dilated veins but was not erythematous. The whole area was surprisingly nontender. Aspiration of the region of maximum swelling yielded pus, confirming the diagnosis of subpectoral abscess.

Incision and drainage were then performed immediately under oxygen and ether anesthesia, the primary incision being placed over the site from which pus had been obtained and extending parallel to the direction of the pectoralis muscle fibers. These fibers were split, giving access to a large abscess cavity extending above almost to the clavicle, medial to the sternum and bulging laterally into the axilla. A large amount of thick yellow pus gushed out. Drains were inserted through counterincisions made in the anterior axilla and on the chest wall into the most dependent parts of the cavity. Bacteriologic studies of the pus showed streptococci.

The patient's general condition improved dramatically, and the temperature dropped gradually, being entirely normal on the 12th postoperative day. There was a short exacerbation of the fever 3 days later, when a hemorrhage followed the removal of a drain and the wound had to be packed. Two or three 1-gm. doses of sulfanilamide but no other chemotherapy, were given at that time.

Postoperatively, the patient stated that 7 or 8 days before admission he had accidentally burned the tip of a finger of the left hand. The resulting blister was cut away, and the finger dressed at the shop dispensary. Subsequently the finger became somewhat tender and painful prior to the development of the acute symptoms described above.

This typical case of acute subpectoral abscess was recognized as a surgical condition before serious extension of the process had occurred. It responded well to adequate incision and drainage without the benefit of chemotherapy.

**CASE 2.** M. D., a 9-year-old schoolgirl, was admitted to the hospital on August 6, 1935. Three weeks previously she

\*Cases of similar infections involving the retroperitoneal iliac lymph nodes secondary to a primary focus in a lower extremity have been observed. The responsible organisms in these cases are usually streptococci and dramatic improvement follows surgical drainage of the retroperitoneal spaces.



had sustained a laceration in the region of the right elbow in a fall. After treatment at home the wound appeared to be healing, but 1 week later, after the child had picked off the scab, the arm became swollen, and she complained of pain in the axilla and developed fever and malaise. She was

temperature continued in its septic course, rising at times to 103°F. The white-cell count at that time was 20,050, with 76 per cent neutrophils. When definite fluctuation was demonstrated in the axilla 2 days later, a subpectoral abscess containing over 75 cc of thin, yellowish pus was drained

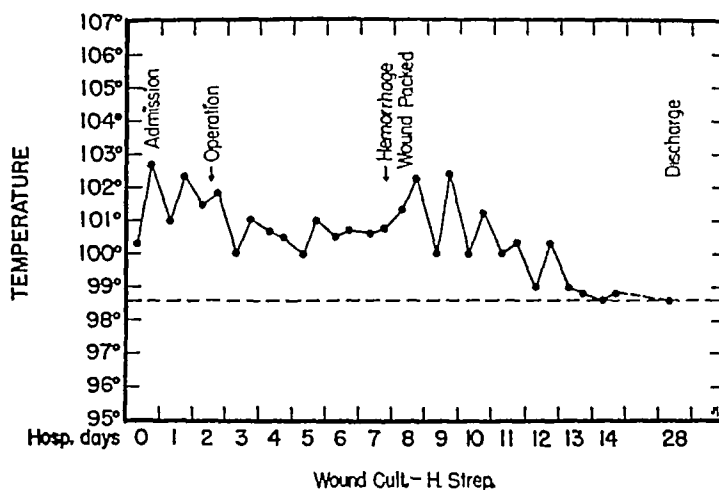


FIGURE 1 Case 1

treated for 1 week or more at home with hot poultices to the axilla, without improvement.

On admission the child appeared sallow and moderately dehydrated. The right arm was held in a position of partial abduction, and shoulder motions were limited in all directions because of the muscle spasm and pain. The right axillary region was tender. Enlarged axillary lymph nodes could be felt, but there was no fluctuation, redness or real

surgically, and a pack inserted. Culture of this pus showed a pure strain of hemolytic streptococcus. The temperature fell to normal within a few hours of the drainage, and the patient made a rapid recovery.

Early recognition of the true lesion in this case would have saved the patient over two weeks of pain and disability.

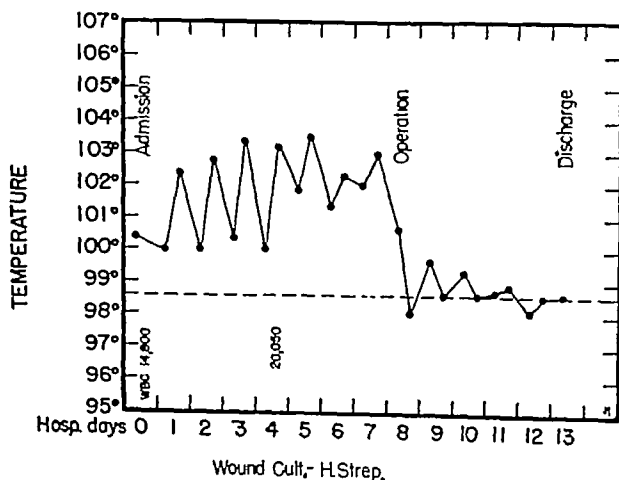


FIGURE 2 Case 2

bulging. A recently healed skin scar was noted over the right olecranon process. The remainder of the physical examination was negative.

The temperature was 100.6°F, the pulse 90, and the respirations 20.

Examination of the blood disclosed a white-cell count of 14,800, with 67 per cent neutrophils. Other laboratory studies were not remarkable. X-ray examination showed a normal chest and no lesion in the bones of the right shoulder girdle.

After 4 days of expectant treatment, swelling of the right pectoral region was apparent, and the right axilla became tender and extremely tender, but never fluctuant. The

CASE 3 H M P, a 28-year-old medical student, was admitted to the hospital on January 23, 1935. Two weeks previously the patient had accidentally pricked the middle finger of the left hand while doing an autopsy. This seemed to heal within a few days, and he was apparently well until 2 days before admission when a pain suddenly developed in the left arm near the shoulder during lifting and became quite severe. During the evening he began to have chills and fever and general malaise. The pain progressed, involving all the left shoulder and the side of the neck. Attempted motion of the shoulder and the left arm was extremely painful.

Physical examination revealed an extremely uncomfortable and moderately toxic patient. The left axillary region seemed slightly swollen and quite tender, and a few small lymph nodes could be felt. The left shoulder anteriorly and the clavicular and pectoral regions were tender to touch. There was only slight swelling in the upper arm and no lymphangitis. A 1-cm healed scar was seen on the dorsum of the left middle finger, with slight redness at its margins. In the absence of actual fluctuation in the axillary region, the attending physicians did not consider surgery to be indicated. The patient continued to experience a great deal of pain in the involved areas and to have fever and chills.

The temperature was 102°F, the pulse 100, and the respirations 25.

A blood culture showed no growth. X-ray films of the shoulder joint and the bones of the shoulder girdle were negative for signs of infection.

On the supposition that this was an acute rheumatic arthritis a course of salicylates was given. The swelling over the anterior aspect of the shoulder and pectoral region increased, and the skin became generally tender to touch, but still fluctuation was absent. The fever continued in its septic course with gradual subsidence to almost normal 10 days after admission. The white-cell count rose, however, to 26,350, with 79 per cent neutrophils on January 28. The pain and the local signs continued, and on February 3, when fluctuation finally became apparent in the anterior axilla, the area was incised with the drainage of 30 cc. of

more of thick, white pus, a culture of which showed hemolytic streptococcus and *Staphylococcus albus*. The fever flared up again, the pain continued, particularly in the upper arm and the white-cell count rose to 34,000. On February 14 surgical drainage of an abscess on the posterior aspect of the left forearm released a great deal of pus. This abscess was found to connect with the original subpectoral abscess cavity. Culture of the forearm cavity showed hemolytic streptococci. The temperature finally reached normal on February 22 as the infected wounds gradually cleared up. Shoulder function returned completely, in time, but the patient noticed a numbness of ulnar nerve distribution in the left hand for over 1 year.

Delay in surgical drainage of the subpectoral abscess in this case resulted in local spread of the

phils. The swelling of the right pectoral region also increased. Some swelling appeared in the axilla and spread to the right shoulder and supraclavicular regions. The patient was then given 25,000 units of penicillin every 3 hours intramuscularly. The temperature, however, continued between 103° and 104°F, and there was no improvement otherwise. The question of pneumonia was raised, but x-ray examination of the chest was negative.

When seen in surgical consultation by one of us (K. B. L.) 2 days after admission the patient was thought to have an acute suppurative lymphadenitis or possibly actual abscess formation in the subpectoral region and was therefore transferred to the main hospital on the afternoon of February 1, for incision and drainage. As a further trial of conservative therapy, the penicillin was continued overnight in doses of 50,000 units intramuscularly every 3 hours. On the following morning, although the temperature had dropped slightly

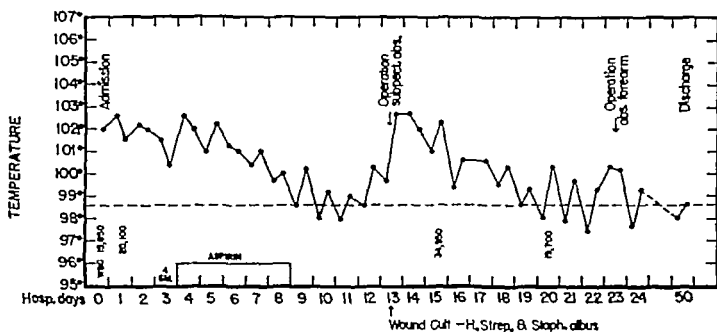


FIGURE 3 Case 3

suppurative process, eventually requiring multiple incisions and a prolonged recovery period. Surgery was deferred until actual fluctuation appeared.

**CASE 4** G. C., a 17-year-old boy, was admitted to the hospital on January 30, 1946. Three days previously the patient had accidentally scraped some skin from the knuckle of the right middle finger. On the following day he was able to squeeze a little pus from the wound, and that night developed malaise, insomnia and a mild chill with fever. He gradually became sicker and on the day before admission the temperature rose to 104.5°F. He vomited and was anorectic. On the morning of admission he was so groggy and toxic and the neck muscles were so stiff and sore that he was thought by his physician to have meningitis and was admitted to the Contagious Department of the Massachusetts Memorial Hospitals.

Physical examination showed considerable pain in the right shoulder region, and the patient appeared quite drowsy. There was moderate swelling over the pectoral region, with tenderness on deep palpation. The right arm was held in slight abduction and motion in general particularly further abduction was painful. There was some stiffness of the neck muscles, particularly on the right side. There was a recently healed abrasion of the skin on the dorsum of the right middle finger. The remainder of the examination was essentially negative. A lumbar puncture revealed normal fluid.

The temperature was 101.6°F, and the pulse 124. Examination of the blood disclosed a white-cell count of 13,050 with 90 per cent neutrophils. The urine gave a +++ test for ketone bodies but was otherwise normal. The temperature rose gradually to 105°F within 36 hours and the white-cell count to 15,700 with 91 per cent neutro-

phils. The swelling of the right pectoral region also increased. The patient not only felt unimproved but also complained of increased pain with some pain extending into the left upper chest wall and over the clavicle. Edema had spread slightly to this, which was tender to touch.

In view of the lack of improvement after 60 hours of intramuscular penicillin and for fear that the infection was about to penetrate into the mediastinum, incision and drainage of the right subpectoral space were done under endotracheal nitrous oxide and ether anesthesia. A mass of edematous lymph nodes and fat was found filling this space up along the axillary vascular sheath, and several cubic centimeters of thin pus was liberated. Cigarette drains were inserted. Cultures of the pus revealed a mixed growth of hemolytic streptococcus, a streptococcus with alpha hemolysis and a weakly pigmented hemolytic *Staph. aureus*.

Postoperatively the penicillin was continued in the same dosage every 3 hours and sulfadiazine was given in full dosage by mouth, so that a blood level of 8 to 10 mg per 100 cc. was maintained. The temperature fell dramatically to 100°F within 2 hours of operation and then gradually subsided to normal on the 2nd postoperative day. The clinical symptoms improved nearly as rapidly and the patient was discharged feeling fine, with a nearly normally functioning shoulder and only a slightly draining wound on the 7th postoperative day. The white-cell count at that time was 9000. Within 2 days however the shoulder pain recurred and the patient was readmitted 4 days after discharge with a temperature of 102°F, some toxicity and considerable swelling in the right supraclavicular fossa. The white-cell count at that time was 15,400, with 81 per cent neutrophils. This was considered to represent a flare-up of the infection in the supraclavicular lymph-node group, and not in the subpectoral space. The incision into the sub-

pectoral space was dry and nearly healed, and probing released only a tiny amount of clear serum. The temperature dropped to normal in less than 48 hours on combined treatment with 20,000 units of penicillin every 3 hours and 1 gm. of sulfadiazine every 4 hours. As a safeguard, these drugs were continued for another week, the patient then being discharged cured.

This case represented fulminating suppurative axillary lymphadenitis relieved promptly by early recognition and surgical drainage. Despite intensive administration of penicillin, surgical drainage was necessary to control the principal focus of infection.

CASE 5 R S, a 22-year-old man, was admitted to the hospital on March 17, 1941. Two days previously he had

100°F, where it remained for 5 days. This was thought to be due to a thrombophlebitis of the right axillary and brachial veins that had become apparent at that time. Swelling and soreness of the arm and shoulder subsided with elevation of the arm and moist heat treatment. The patient was discharged on the 16th postoperative day, with only minimal residual disability of the shoulder and arm.

In this case an acute subpectoral lymphadenitis, apparently due to an organism of low virulence, was encountered. No primary focus was found.

CASE 6 A M, a 19-year-old boy, was admitted to the hospital on July 31, 1933. The patient had first noted pain in the right axilla 11 days previously, followed by swelling throughout the upper arm, the shoulder region and the axilla. The pain then became excruciating, particularly on motion.

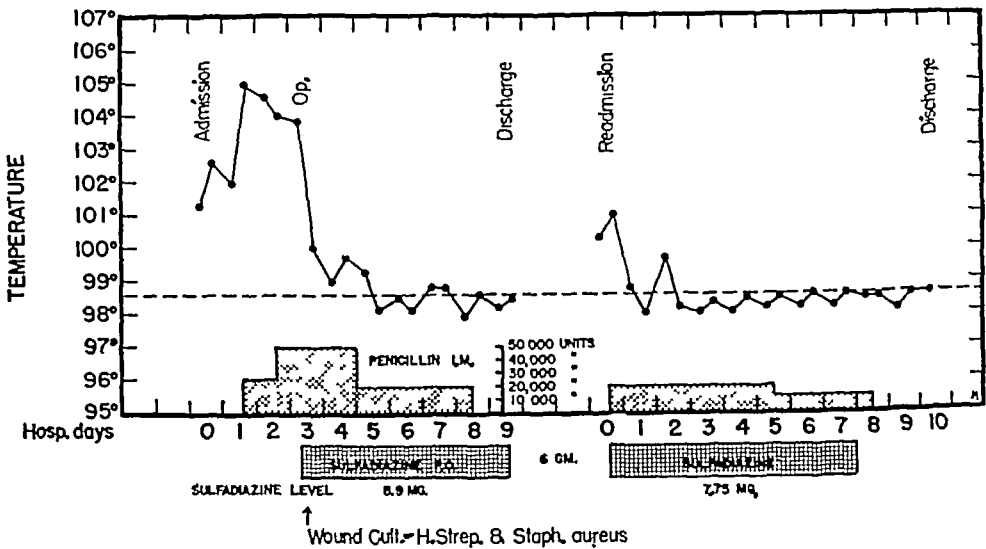


FIGURE 4 Case 4

first noticed pain and swelling of the right shoulder region and upper arm but had felt well otherwise. On the day before admission the swelling extended to the pectoral region, and motion of the shoulder became painful. That evening he had fever without chills. There was no history of trauma or of antecedent infection of any sort.

On physical examination the patient appeared slightly toxic and rather uncomfortable. There was a pronounced swelling, without erythema or edema of the skin, over the entire right pectoral area and to a lesser extent in the axilla and over the region of the anterior shoulder and lower neck. The arm was held at about 20° of abduction, and such movement was painful. Two slightly enlarged tender lymph nodes were felt in the lateral axilla (brachial nodes).

The temperature was 102°F and the pulse 96. Examination of the blood disclosed a white-cell count of 13,000, with 79 per cent neutrophils. The blood chemical findings and other laboratory studies were normal. X-ray examination of the shoulder girdle showed no evidence of diseased bones or joints. A diagnosis of acute subpectoral abscess or suppurative lymphadenitis was made within a few hours of admission.

Incision was promptly performed by one of us (K. B. L.), revealing an acute edematous mass of lymph nodes in the subpectoral space. This space was thoroughly opened up by incision both through the axilla and down through the subpectoral muscles over the point of maximum swelling. Bacteriologic examination of material from the wound showed a pure culture of *Bacillus subtilis*. The pain was promptly relieved by this procedure. The temperature fell gradually to normal in 48 hours, without a definite purulent discharge at any time. The temperature then rose again to

of the shoulder. The patient became anorexic, somewhat toxic and feverish. Three weeks before admission, 10 days before onset of the symptoms, he had noted a small furuncle just to the right of the sternum, which he had squeezed several times, but later this had seemed to heal.

Physical examination revealed a small, nearly healed furuncle near the sternum. A large, tender, moderately reddened swelling was noted in the region of the right pectoralis major muscles.

The temperature was 100.6°F. Examination of the blood disclosed a white-cell count of 13,300, with 83 per cent neutrophils. The urine showed slight trace of albumin, and the sediment contained rare white cells and a few red cells. X-ray examination of the lung fields was negative.

On the following day a large right subpectoral abscess was incised and drained through the axillary route. A large mass of blood clots with some inflammatory tissue and definite pus was found in the space. This was cleaned out and a gauze pack was inserted. A culture of the fluid revealed a hemolytic *Staph aureus*. On the evening of the day of operation the temperature was 99°F and thereafter was normal. The patient was discharged on the 7th postoperative day, having made a good recovery.

The infection in this case, which was due to staphylococcus, was definitely less acute and severe than the streptococcal infections described above. Incision and drainage of the abscess resulted in prompt relief, although the patient could have

been saved a week or more of pain and invalidism by an earlier diagnosis

### SUMMARY

A series of 6 cases of acute subpectoral abscess or suppurative lymphadenitis, usually secondary to minor infections in the upper extremity, is reported. This infection is more toxic when due to streptococci than when due to staphylococci or other organisms.

Demonstrable fluctuation is regarded as a late and uncertain manifestation of this syndrome, presumably because the involved lymph nodes may be slow to suppurate and because the abscess when formed is enclosed in a tough fascial envelope deep beneath the pectoral muscles.

Early incision and drainage, which provide the treatment of choice, prevent the extension of the

suppurative process to other regions and bring about rapid subsidence of the infection and almost immediate relief of pain.

Sulfonamide and antibiotic therapy is a valuable adjunct to surgery in this condition, but cannot be relied on to control the infection alone.

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## ECZEMA VACCINATUM

### Report of a Case

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UNTOWARD reactions following vaccination are rare. The clinical entity known as eczema vaccinatum, a type of generalized vaccinia, is one such complication. According to estimates, generalized vaccinia occurs in the ratio of 1 case to 20,000 or 40,000 vaccinations.<sup>1</sup> Because of its rarity, the diagnosis may not be readily apparent. Occasionally, the admission of a patient with unrecognized eczema vaccinatum to the skin ward of a hospital results in an outbreak among those exposed.<sup>2</sup>

Generalized vaccinia is the term applied to the generalized eruption of typical vaccinal lesions that occur after vaccination. It varies in degree from a mild illness with a few scattered lesions to a severe fatal infection and a clinical course similar to that of smallpox. Eczema vaccinatum occurs for the most part in children with chronic skin disease who have been exposed to cow-pox virus either by vaccination or by contact with a vaccinated person.

It is the purpose of this discussion to present the clinical and laboratory findings in a recent case of eczema vaccinatum. The clinical diagnosis was confirmed by a positive Paul test. Treatment with penicillin, which had been instituted before the illness had been diagnosed, was continued, the purpose being to minimize the possible effects of secondary invaders.

S. H., a 2-year-old boy, was admitted to the hospital on May 3, 1946, because of an exacerbation of a cutaneous eruption that had been present for about 6 weeks. The family physician, who was treating the child for eczema of the flexor surface of both elbows and knees, reported that tiny pearl-like lesions had appeared at the periphery of the eczematous areas 4 days before admission. Two days later the lesions had spread over the entire areas previously involved in the eczema. The mother noted flushing of the face and the child appeared quite ill. An older sibling had been vaccinated 13 days before unusual signs and symptoms had been noticed in this patient.

Physical examination revealed a well-nourished child who did not appear to be extremely toxic. There was generalized lymphadenopathy. Over the skin of both antecubital and popliteal areas individual lesions had coalesced into a grayish purulent mass (Fig. 1 and 2). At the periphery the pustules were discrete and extended over both arms to the wrists. A few discrete umbilicated pustules were present over the face and lids and in the hair. Physical examination was otherwise negative.

The temperature was 103.4°F, the pulse 110, and the respirations 24.

The red-cell counts on May 4 and 7 were 3,200,000 and 3,540,000 respectively and the hemoglobin determinations on the same days were 10.2 and 12.1 gm. The white counts from May 3 to May 7 varied from 12,500 to 22,400. A smear on May 7 showed 62 per cent neutrophils, 30 per cent lymphocytes, 1 per cent monocytes and 7 per cent eosinophils. A urinalysis on May 4 was negative. A sulfadiazine level of 6.8 mg. per 100 cc. was reported on May 7. A culture from a draining lesion revealed a nonhemolytic *Staphylococcus aureus*.

Scraper smears of the cornea of a rabbit with scrapings of lesions taken on May 6 revealed Guarnieri bodies in epithelial cells scraped from the eye 3 days after inoculation (Fig. 3).

The temperature rose to 105.4°F on the day of admission and fluctuated between 100 and 105°F until May 9. On May 7 several new pustules appeared on the face, legs and

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The Paul test was performed by Dr. Frederic Parker, Jr., pathologist, M. H. Mallory Institute of Pathology, Boston City Hospital.

trunk. On the following day there was a moderate amount of purulent drainage from the lesions in the popliteal and antecubital areas. During that time the patient had become irritable and restless, crying out frequently. As the pustules

has also been noted to Kaposi's varicelliform eruption. Since the first description of this skin disease by Kaposi<sup>4</sup> there has been a great deal of disagree-

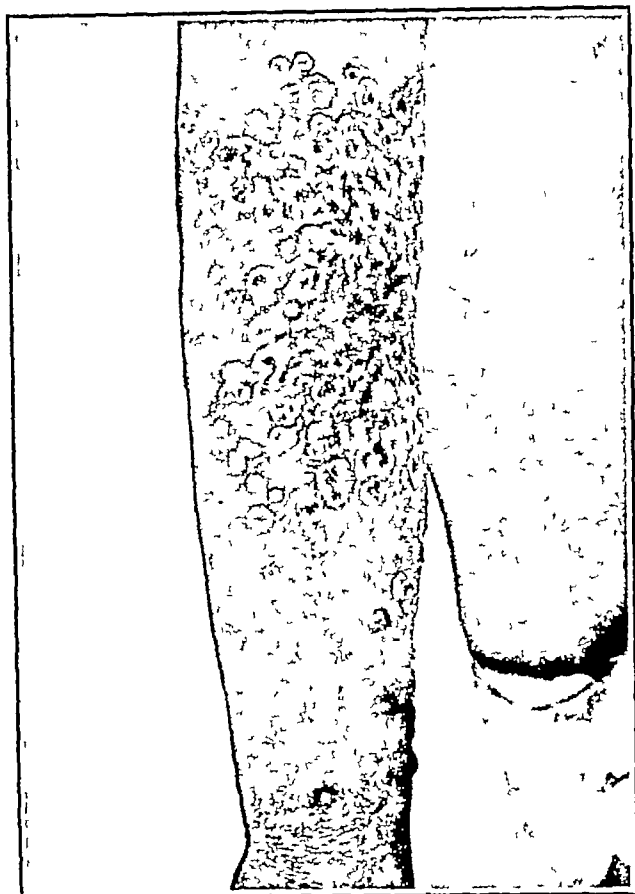


FIGURE 1 *Vaccinal Lesions in the Antecubital Space of the Right Arm*

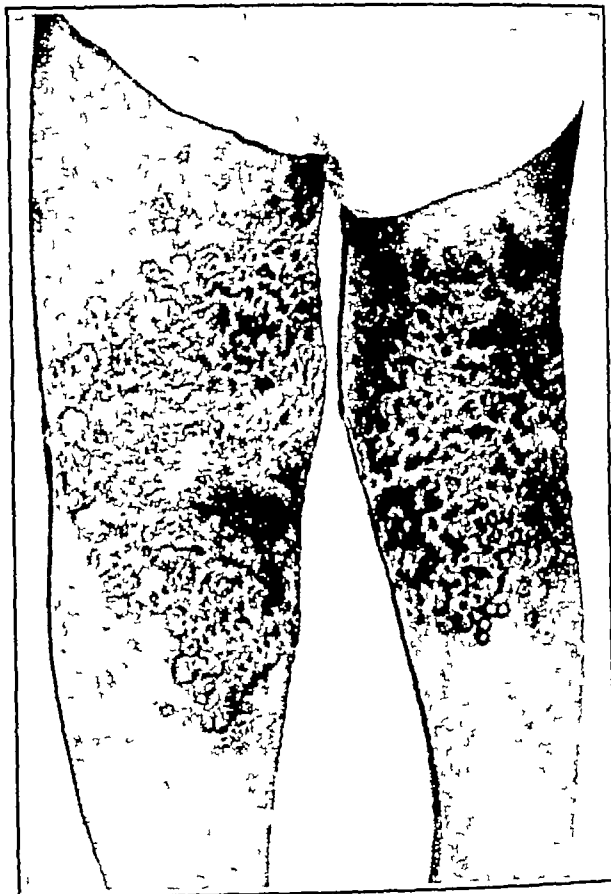


FIGURE 2 *Vaccinal Lesions in the Popliteal Spaces*

dried and scabs formed, the drainage changed from a purulent to a serous exudate and gradually disappeared.

Treatment with penicillin and sulfadiazine was started on admission. Penicillin was administered in a dosage of 10,000 units every 4 hours until May 12, and sulfadiazine in a dosage of 0.5 gm every 4 hours. Chemotherapy was halted on May 7, when a morbilliform eruption appeared on the face and anterior and posterior aspects of the chest. The temperature fell to 98.9°F on May 10 and except for a rise to 102°F on May 12, remained normal thereafter. Recovery was uneventful. No scars were noted at an examination several months later.

Although this patient had not slept in the same bed with the vaccinated child, no attempt at segregation had been made, and there was ample opportunity for direct contact between the children. In addition to direct contact, however, infection of the skin of the eczematous patient by droplet infection must also be borne in mind. In 1929 vaccine virus was demonstrated in the upper respiratory tract four or five days after vaccination.<sup>3</sup> Increased susceptibility of patients with skin disease to vaccine virus is well known. In the case reported above the patient himself had not been vaccinated.

Heightened susceptibility of eczematous children

ment concerning its causation and relation to eczema vaccinatum. When there has been no

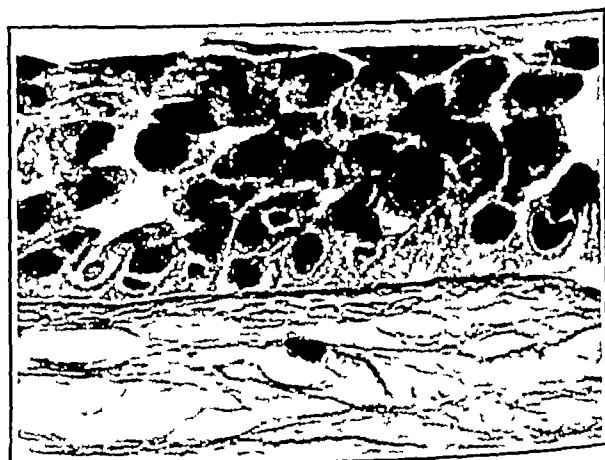


FIGURE 3 *Photomicrograph Showing Guarnieri Bodies in the Epithelial Cells of the Rabbit's Cornea*

history of vaccination or of contact with a recently vaccinated person, the diagnosis of Kaposi's vari-

celliform eruption is usually made. The isolation of herpes virus from patients ill with the latter infection<sup>4-7</sup> has differentiated it from eczema vaccinatum, which is of course due to the vaccine virus.

Outbreaks of both eczema vaccinatum and Kaposi's varicelliform eruption have occurred on skin wards following the admission of patients suffering from this infection. Danziger<sup>2</sup> reported such an outbreak on the open ward of an infants' hospital in which 5 out of 6 children with skin disorders contracted vaccinia after the introduction of a patient with generalized vaccinia. McLachlan and Gillespie<sup>8</sup> described an outbreak of Kaposi's varicelliform eruption in which 16 cases occurred in a dermatologic ward under similar circumstances.

Chemotherapy has been employed in the treatment of both infections for its possible effect on secondary invaders. For the same reason penicillin was used in the treatment of the patient described above.

A case fatality rate of 33 per cent has been reported for eczema vaccinatum.<sup>9</sup> Although the clinical course is mild in some cases, patients whose illness is complicated by secondary pneumonia or severe skin infection may be quite ill. It is possible that penicillin has considerable influence in reducing the high case fatality rates associated with eczema vaccinatum.

One or two simple precautions concerning vaccinations must be re-emphasized. Vaccination should be deferred on patients with skin disorders until

recovery has occurred. Vaccinated persons should not be allowed to be exposed to patients suffering from skin infections. If these simple rules are observed the exceedingly low incidence of generalized vaccinia will be reduced to an even greater extent.

### SUMMARY

A case of eczema vaccinatum is presented in which the infection occurred as a result of contact with a vaccinated sibling. The clinical diagnosis was confirmed by a positive Paul test.

Precautionary measures, such as deferring vaccination of patients with skin disorders and preventing exposure of such patients to vaccinated persons, will reduce to an even greater extent the present low incidence of generalized vaccinia.

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## SUBPHRENIC ABSCESS FOLLOWING PRIMARY CLOSURE FOR PILONIDAL SINUS\*

## Report of a Case

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THE problem of the proper management of pilonidal sinus has occupied a position of increasing importance in the medical literature in the past six years. In the medical care of an active military force of several million generally healthy men and women, pilonidal cyst and sinus have been among the most frequent surgical causes of disability. It is the purpose of this communication to indicate some of the hazards attendant on the primary closure of pilonidal wounds.

Before the war the surgical procedure in widest usage was radical excision, a granulating wound being left to heal by secondary intention. Primary closure of a pilonidal wound had been advocated by some but in general had been given up because of a disturbing number of recurrences (or so-called "persistences") and an occasional severe infection in the sutured wound. Contributing to these complications were the tendency to limit the extent of the excision to preserve tissue for the closure, technical difficulties in obliterating the dead space, the location of the operative field in a region prone to perspire freely and in proximity to the rectum and anus, and perhaps a failure adequately to evaluate the extent of inflammatory changes present at the time of operation.

With the advent of chemotherapy—first, the sulfonamides, followed by penicillin and more recently by streptomycin—there occurred renewed interest in attempts at primary suture of the pilonidal wound. This approach received a tremendous impetus during the war years, when it was considered important to eliminate the loss of time necessary for the healing of a granulating wound. The objective of returning a man to active duty as soon as possible led to a policy of primary closure in a large proportion of cases in almost every service hospital. The ready availability of the chemotherapeutic agents for the control of infection lent courage to these efforts.

That no single method of primary suture has been pre-eminently successful is evidenced by the great number and variety of procedures devised to meet the problem. One of the most promising techniques for obliterating the dead space is that of utilizing gluteal muscle—fascial flaps, as described by Pope<sup>1</sup> and further reported by Holman.<sup>2</sup> The latter advocates avoiding skin-penetrating sutures and completes the closure with a subcuticular

stitch of wire or dermol. The use of silk is recommended by Dunphy and Matson.<sup>3</sup> Cotton has been employed by Ziegler et al.<sup>4</sup> and Larkin<sup>5</sup> finds stainless steel the material of choice. All these authors stress the value of meticulous operative technique and care in the postoperative management in lowering the recurrence rate, whether primary closure has been performed or the wound permitted to heal by granulation. There is general agreement that only about 60 per cent of cases are suitable for primary closure and that the recurrence rate with primary closure is slightly higher than that with the more tedious granulating process. Burns,<sup>6</sup> in a study of civilian cases, reports some success with various methods of closure but finds that the most generally effective results have been obtained by permitting the wounds to granulate. It is difficult to evaluate the end results among service personnel because of the limitations imposed by military conditions on an adequate follow-up study.

The emphasis on primary closure and the protection afforded by chemotherapy have tended to minimize the potential risk entailed in this procedure. The following case, in which a fatal result from overwhelming infection was averted by a narrow margin, is an example in point. The multiple operations were performed by various members of the surgical service of a large naval hospital.

W. R., a 17-year-old seaman, entered the hospital on March 5, 1945, because of a small draining sinus in the intergluteal cleft, with a narrow surrounding area of induration. Under treatment with Sitz baths the inflammatory reaction subsided rapidly, and drainage from the sinus ceased. Ten days after admission, under procaine spinal anesthesia, the cyst was excised en bloc, together with an ellipse of overlying skin. The cyst extended to the lower end of the coccyx and penetrated the coccygeal bone for a short distance. The fascia was closed with interrupted sutures of chromic catgut. Skin closure was performed with figure-of-8 sutures of No. 32 steel wire, and the wound was not drained.

Two days after operation the temperature rose to 102°F, associated with wound pain and tenderness. The sutures were removed, and the infected wound was packed widely open. During the next 4 days discharge from the wound became profuse and foul-smelling, the temperature rose to 104°F, associated with a pain in the right posterior portion of the chest. On the 5th postoperative day there was marked peripheral collapse and delirium, the pulse was 138, the respirations 55, and the blood pressure 80/60. The chest pain continued, but there was no cough or expectoration, and there were no abnormal physical signs referable to the thorax. The abdomen was rigid, and there was no pain, tenderness or vomiting, flatus and loose stools were passed. There was no pain or tenderness of the extremities. The white-cell count was 13,800, with 71 per cent neutrophils and 12 per cent band forms, the hemoglobin was 13.5 gm. A roentgenogram of the chest showed clouding of the right lower-lung field.

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The patient ran a septic course with swinging temperatures to 106°F and marked rapid deterioration in his general condition. At no time were shaking chills noted and blood cultures were consistently negative for both aerobic and anaerobic organisms. Intensive supportive therapy included maintenance of fluid and electrolyte balance by means of parenteral fluids containing glucose salt, vitamins calcium, plasma and Amigen, fourteen transfusions of whole blood and oxygen. Chemotherapy consisted of 20,000 units of penicillin every 2 hours intramuscularly supplemented by 40,000 units of penicillin and 6 gm of sodium sulfadiazine by the intravenous route daily. The total amount of penicillin given was 8,100,000 units and that of sulfadiazine 120 gm.

It was the clinical impression that a retroperitoneal cellulitis accounted for the extreme toxicity and abdominal rigidity. An indurated area in the right infrascapular region was incised on April 5, and necrotic foul-smelling tissue was encountered. On April 28 there was a sudden profuse drainage of foul-smelling greenish yellow pus from this wound. Roentgenograms showed pooling of lipiodol in the right subphrenic space. Fluoroscopy demonstrated that the right leaf of the diaphragm was elevated and fixed. A diffuse haze occupied the right lower-lung field.

The diagnosis of a large right subphrenic abscess was then established. Expectoration of foul-smelling material similar to that on the dressings indicated a bronchopleural fistula. On May 2 an incision was made in the right mid-axillary line over the ninth interspace. The pleura was pushed aside, the fibers of the diaphragm were separated with a clamp and a large quantity of foul-smelling yellow grey pus was evacuated. This was positive on culture for *Escherichia coli*, *Streptococcus faecalis* and *Staphylococcus aureus*. Copious amounts of pus drained from this site for 2 weeks, and the temperature elevations fell to between 102° and 103°F. The expectoration of purulent material promptly ceased and did not recur. On July 27 a thoracotomy and rib resection were performed, a chronic empyema sinus being unroofed. After this procedure the patient became afebrile, and there was rapid and steady improvement. By November 15 all the wounds had healed and the weight had risen to 158 pounds from a low of 104 pounds. The pilonidal wound had been completely epithelialized within 3 months of the original operation. The patient was discharged from the hospital 1 year after an operation generally classified in the "minor" category. A follow up letter 10 months later disclosed that he was experiencing no restriction of his activities there had been no recurrence of the pilonidal cyst.

It is apparent that any operative procedure that possibly entails the sequelae experienced in the case presented above is not to be considered lightly. It may be contended that this case was not suitable for primary closure, yet the inflammation present on admission was only moderate in degree and subsided rapidly before the operation was undertaken. The objections that chemotherapy should have been instituted before operation and that larger doses should subsequently have been exhibited may be valid. The combination of *Esch. coli*, *Str. faecalis* and *Staph. aureus*, however, is one

against which it would be difficult to issue a guarantee of protection with the means currently available. Contamination of the wound presumably occurred as the result of injury to the rectum, either during the process of mobilization of the cyst or in the placing of the deeper sutures. Such an accident may easily pass unnoticed.

Sweeping conclusions regarding the merit of a surgical procedure would certainly be hazardous on the basis of a single accident such as this. Careful selection of cases, meticulous operative technique and the judicious exhibition of chemotherapeutic agents may all contribute to the elimination of a large part of the risk incurred when primary closure of a pilonidal wound has been performed. It is suggested, however, that packing the wound widely open and permitting healing by granulation be considered the method of choice in the hands of the inexperienced operator or when there is any evidence of recent inflammation in the local lesion.

### SUMMARY

A case of pilonidal sinus treated by excision and primary closure is presented.

The postoperative course was characterized by a fulminating retroperitoneal cellulitis, right subphrenic abscess, bronchopleural fistula and empyema. Although recovery was ultimately effected, a fatal issue was narrowly averted.

It is suggested that the primary closure of pilonidal wounds be reserved for cases conforming to limited criteria. In the hands of the less experienced surgeon, or in the presence of recent inflammation, the procedure of total excision, packing the wound widely open and permitting healing by granulation may be indicated.

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## MEDICAL PROGRESS

### CHEMICAL FACTORS IN ASTHMA (Concluded)\*

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#### BLOOD SUGAR

Numerous investigators have thought that there might be a disturbance in the metabolism of sugar in patients suffering from asthma and allergic conditions. In 1924 Ramirez, St. George and Moses<sup>43</sup> examined the levels of the blood sugar in 40 patients, 28 of whom had asthma and hay fever. Determinations were made before and after treatment, but they revealed no uniform differences in the levels of the blood sugar at these two periods.

In 1929 Malone<sup>44</sup> found the average fasting level of blood sugar to be 75.4 mg per 100 cc in 15 patients with allergic asthma associated with food sensitivity. In 1933 Black<sup>45</sup> reported an average fasting blood sugar level of 78.9 mg per 100 cc in 100 patients who had a definite history of allergy, and he concluded that more than half the patients with hay fever and asthma have fasting blood sugar values below the normal range and that the sugar tolerance is definitely elevated.

In 1936 MacQuiddy, McIntyre and Koser<sup>46</sup> published their findings of fasting blood sugar levels and tolerance curves on 20 patients with asthma and hay fever and 21 normal subjects used as controls. They found no significant difference between the two groups. In 1937 Wagner and Rackemann<sup>47</sup> studied the blood sugar in 24 patients with asthma and hay fever, using both venous and capillary bloods. In all cases the fasting blood sugar and the glucose-tolerance curves were essentially normal.

In 1939 Waldbott, Ascher and Rosenzweig<sup>48</sup> attempted to make a more crucial study. They selected a group of 14 patients sensitive to pollen who were given a slight overdose of pollen extract. During the mild general reaction that supervened, the blood sugar was determined at intervals of fifteen minutes. The values showed an immediate transient rise followed by a prolonged fall to an average level of 63 mg per 100 cc, which took over two hours to return to the basic level. When the same procedure was carried out on 24 patients who did not develop any reaction to the pollen dose, the blood sugar remained steady. Also, in 22 nonallergic persons who were given pollen injections corresponding to the amounts received by the allergic group, the blood sugar did not change.

In 1939 Joseph<sup>49</sup> had a different concept. He treated 104 patients, of whom 96 had asthma and

34 had arthritis or arthrosis, with eight to twelve daily injections of 8 units of insulin, and he claimed that the patients improved.

In 1941 Abrahamson<sup>50</sup> suggested a reciprocal relation between asthma and diabetes. Asthma patients were made worse by sodium chloride, and diabetic patients better, the former were prone to hypothyroidism, and were relieved if they developed hyperthyroidism, the reverse being true for the latter. The two diseases, although frequently occurring among members of the same family, were mutually exclusive and were rarely observed in the same person at the same time. Asthma attacks occurred with a tendency to hypoglycemia, and drugs relieving asthma raised the level of blood sugar. The author assumed that bronchial asthma was associated with hyperinsulinism, as the glucose-tolerance curves of 12 patients with asthma corresponded to those found in cases of hyperinsulinism. The patients improved on high-fat, low-carbohydrate diet, and this fact was supposed to justify the claim that hyperinsulinism was one of the conditions necessary for the appearance of asthmatic attacks. It was a logical explanation for the frequency of nocturnal asthma attacks when the blood sugar level was low, and it explained the failure of glucose to effect a last remission. Vollmer,<sup>51</sup> on the other hand, in 1935 had treated 7 children with severe asthma with a course of fifteen to twenty-five injections of insulin, the doses being regulated for each child so that the symptoms of shock were not too severe. Most children were at least temporarily benefited—especially those treated at home with no change in environment. This improvement was attributed to secondary endogenous production of adrenaline, which improved the asthmatic symptoms. Others have also claimed improvement of asthma by the use of insulin shock therapy.

The evidence cited so far does not show that a low blood sugar level is a cause of the asthma attack. The figures of Malone<sup>44</sup> and Black<sup>45</sup> do not fall below 70 mg per 100 cc, which is generally accepted as the point below which a state of hypoglycemia exists. Falling blood sugar values and allergic shock could also occur in almost any type of shock. How low is the blood sugar at the onset of a nocturnal attack of asthma? Patients with asthma who miss a meal during the day probably have a fall in blood sugar but do not necessarily suffer an acute attack of asthma.

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lthough blood sugar levels in patients have not been reported at the time when a severe attack occurs, these persons are often unable to eat, and consequently the blood sugar must fall, this, however, is a result rather than a cause of the asthma. Again, why should injections of insulin or insulin-shock therapy improve asthma when the effect is a hypoglycemia? There is no proof that such improvement does take place, Joseph's<sup>44</sup> patients probably gained in health because of a better appetite. No regular schedule of injections of insulin was maintained, levels of the blood sugar were not followed regularly, no glucose tolerance tests were done, and some patients had other forms of treatment as well. Thus, the answer to the causes of asthma is not likely to be concerned directly with the blood sugar level.

### CHOLESTEROL AND FAT METABOLISM

Cholesterol is an essential constituent of all cells and fluids of the body. It is concerned with the metabolism of fat, and a disturbance in the metabolism of fat has been considered a factor in the cause of eczema. In 1933 Hansen<sup>45</sup> studied the blood content of cholesterol and fatty acids in 5 normal infants and in 6 infants with eczema. The levels of cholesterol and total fatty acids in the blood serum were slightly less in the cases of eczema than in the control infants, although still within the normal range. The average iodine number of the serum fatty acids in the eczema group was 84, and in the control group 111, indicating that the serum fatty acids were less unsaturated in infantile eczema than in the control infants. The author assumed that unsaturated fatty acids played a role in the etiology of infantile eczema. In 1936 Bullen and Bloor<sup>46</sup> determined the total fatty acids, the cholesterol fatty acids and the iodine number — by the same method that Hansen<sup>45</sup> had used — on 14 patients with hay fever or asthma who also had had eczema in infancy and on 12 nonsensitive subjects in the same age group. The averages of the results were nearly identical in the two groups. There was no definite difference in the degree of unsaturation of the plasma fatty acids. Thus, the feeding of unsaturated fats appears to be of no therapeutic value in asthma and hay fever. Bloor, Blake and Bullen<sup>46</sup> then did further work on the fractions of the total fatty acid, neutral fat, phospholipids and cholesterol esters in 14 patients with asthma, 11 with hay fever, 1 with contact dermatitis and 1 with chronic urticaria, as well as in 5 normal persons. No definite differences were found in the nature of the fatty acids in the three classes of sensitive patients and in the nonsensitive subjects. On the other hand, marked differences were observed in the degree of unsaturation in the three groups of compounds. In the cholesterol esters the fatty acids were much more unsaturated than in the phospholipids or in

the neutral fat, and in the phospholipids the fatty acids were somewhat more unsaturated than in the neutral fat. Cholesterol appears to have a special function in the metabolism of the unsaturated fatty acids, but what this is and what it has to do with allergy the authors do not state.

In 1937 Bruger and his collaborators<sup>44</sup> determined the levels of cholesterol in the bloods of 49 patients with hay fever and 50 patients with asthma under treatment. They found that there was a tendency for the total blood cholesterol to be slightly elevated above the average normal in patients with treated hay fever and slightly below normal in those with treated asthma. In both groups the percentage of free cholesterol in total cholesterol was definitely elevated above the average normal. In 1938 Chobot and Dundy<sup>44</sup> measured the levels of cholesterol in the blood of 35 allergic and 25 nonallergic children and observed that 12 allergic children had values above 200 mg per 100 cc. Since a high blood cholesterol may suggest hypothyroidism, they tried therapy with desiccated thyroid in these children but produced no benefit.

Since the metabolism of cholesterol is so little understood, it would be difficult to say on the evidence at present available that cholesterol is concerned with allergy. The idea that the fat metabolism is concerned with the fundamental nature of allergic sensitivity is an attractive thought, but it cannot be supported as yet. A paper by Burr has suggested that the feeding of linseed oil, which contains predominately unsaturated fatty acids, to infants with atopic eczema is beneficial. This treatment has been given to only a few patients so far, but in most of these the eczema has been improved, and the method deserves further study. One notes that except for Hansen's report, the work on fats in allergy has been done on patients with asthma and hay fever rather than on patients with eczema.

### THE VITAMINS

#### Vitamin C

Another attractive theory about the causes of allergy has been that vitamins play a part — either a deficiency in feeding or a faulty absorption and utilization. Ascorbic acid is a reducing agent and is believed to function as a respiratory catalyst in oxidation phenomena in the cells of the body tissues. In 1936 Solomonica<sup>47</sup> claimed that vitamin C administered prior to sensitization with horse serum protected guinea pigs against anaphylactic shock. In contrast, however, Dragstedt, Eyer and Ramirez<sup>48</sup> failed to show that vitamin C protected dogs against peptone shock or against anaphylactic shock after sensitization with horse serum. In a series of experiments with guinea pigs Van Niekerk<sup>49</sup> concluded that a deficiency of vitamin C had no influence on the development of anaphylactic sensitization to horse serum. Preliminary

treatment with vitamin C did not protect the animals against shock, nor did the addition of vitamin C to the horse serum hamper the shock action. In a different experiment Cohen<sup>60</sup> reported that vitamin C deficiency induced by feeding 25 guinea pigs only 20 to 64 per cent of the daily requirement did not prevent the development of anaphylaxis.

Beginning about 1938, ascorbic acid was used rather widely in the treatment of patients with allergic symptoms. Hunt<sup>61</sup> treated 25 patients with asthma with 100 mg of ascorbic acid daily for several weeks, those with acute symptoms were given 500 mg parenterally. In no case was any improvement noted in the amount of wheezing, in the incidence of attacks or in the general condition. In 1941 Goldsmith, Ogaard and Gowe<sup>62</sup> found the fasting blood level of ascorbic acid in 29 patients with bronchial asthma to be  $0.410 \pm 0.051$  mg per 100 cc, a subnormal level being found in 19 cases, the level in a control group was  $0.602 \pm 0.049$  mg per 100 cc. During a period of several months on a standardized regimen 6 of 7 patients with bronchial asthma were unable to maintain a blood ascorbic acid level of 1.0 mg per 100 cc or more, whereas members of a control group maintained such a level in most cases. These findings were interpreted as indicating that there is an increased requirement for vitamin C in patients with asthma.

In 1942 Holmes and Alexander<sup>63</sup> found the urinary output of vitamin C in 25 patients with hay fever (10 mg per 100 cc) to be below the amount excreted by average healthy persons (30 to 50 mg per 100 cc). This indicated a low level of vitamin C in the body, which was probably due to inactivation or destruction of the vitamin. On treatment with 100 to 500 mg of vitamin C daily 88 per cent of the patients reported a gain in health. Pollen counts continued to be high during the period of study. Hebal<sup>64</sup> treated 9 proved cases of hay fever with 500 mg of vitamin C daily and noted no beneficial effects. He did no determinations of the vitamin C levels in blood serum and urine, and the patients had no other form of treatment at the time the study was done. Friedlaender and Feinberg<sup>65</sup> treated 43 patients with hay fever with 500 mg of vitamin C daily and observed no beneficial results. Blood levels of vitamin C were determined on patients with and without vitamin C therapy, and were found to be within the normal range. Large doses of vitamin C produced the usual saturation blood levels of 1 mg per 100 cc. Ruskin,<sup>66</sup> in 1945, reported 27 cases of hay fever and asthma treated in 1944 with 250 to 750 mg of vitamin C daily by mouth. Of these, 20 (74 per cent) were improved, although the pollen count was higher in 1944 than in 1943. Nine of 11 patients receiving desensitization also reported that their symptoms were milder while they were taking the vitamin C. The author concluded that vitamin C was valuable in allergy — even superior to desensitization — and that allergic

disturbances were related to nutritional deficiencies, primarily that of ascorbic acid.

Niacin is believed to be a component of coenzymes that act in glycolysis and cellular respiration; it also acts as a vasodilator and increases circulation of the blood. In 1941 Maisel and Somkin<sup>67</sup> treated 21 patients having severe asthmatic paroxysms with 0.1 gm of niacin intravenously and produced relief of symptoms in 16 patients. Of 9 chronic asthmatic patients who received 0.2-gm doses of niacin orally, 5 were benefited. The authors do not know the exact mechanism of action of niacin in these cases, but they had no reason to believe that a vitamin deficiency existed. In 1941 Melton<sup>68</sup> gave 50 or 100 mg of niacin intravenously to 19 patients during acute paroxysms, with definite improvement in 16 cases. The drug was also given orally in doses of 50 to 100 mg two or three times daily to 30 patients who had frequent paroxysms. Frequency and severity of attacks were reduced in 16 cases. Flushing and other symptoms produced by niacin appeared in some cases. The authors thought that the action of the drug in dilating blood vessels was accompanied by a similar action on bronchioles.

In general, then, one must observe that patients with asthma are often undernourished and require an increased amount of vitamins for recovery of general health. In addition, it must not be forgotten that in other conditions in which metabolism is increased, such as prolonged exercise, infection and chronic debilitating diseases, more vitamins are required by the body. Many nonallergic persons with low levels of vitamins in the body experience a gain in health on treatment with large doses of these vitamins. Ruskin<sup>66</sup> did not make a control series of cases treated by desensitization alone; he did not discuss the general health of his patients, their dietary habits or changes in weight. His proof that vitamin C therapy in these patients was the dominant factor in the improvement was therefore not conclusive. The action of niacin on asthma does not seem to be on a basis of vitamin deficiency, but is possibly due to its vasodilator effect. Deficiencies of vitamin C or niacin, if present, are probably not contributory causes of asthma, but when present they may aggravate asthma which already exists.

#### OTHER CAUSES OF ASTHMA

In 1940 Evans and Bodman<sup>69</sup> developed an interesting theory — that the cause of allergic manifestations involved the absence of certain catalysts of coenzyme activity. By using an oxidation catalyst — ethylene disulfonate — they attempted to restore the deficiency. They had no objective findings to confirm their theory, and the treatment recommended — ethylene disulfonate — has been shown to be worthless.

Another concept about allergy is much more interesting. In 1936 Selye<sup>70</sup> presented his theory of the adaptation syndrome, which may be defined briefly as the response of the organism to stress or damage to which it is not adapted. The first or shock phase when the patient is subjected to the alarming stimulus is characterized by tachycardia, a decrease in muscular tone and body temperature and a rise and then a fall in the blood pressure and in the blood sugar. There is anuria, acidosis and a discharge of adrenaline from the adrenal medulla. With these go certain other changes, such as hemoconcentration, edema formation, leukopenia followed by leukocytosis, negative nitrogen balance and chemical changes in the blood, including an increase in nonprotein nitrogen, potassium, phosphate and globulin and a decrease in the blood chloride. The shock phase is followed by the countershock phase in which the subject begins to develop resistance to the damaging agent. There is enlargement of the adrenal cortex and a general reversal of the changes occurring in the shock phase, with an increase in production of corticoid hormones from the adrenal cortex accompanied by a decrease in urinary excretion of 17 ketosteroids. Thirdly, there is the stage of resistance, and finally the stage of exhaustion. Selye<sup>71</sup> calls conditions in which these changes occur "diseases of adaptation" and cites as examples hypertension, nephrosclerosis, rheumatic fever, periarteritis nodosa and gastrointestinal ulcers.

This idea of Selye is pertinent to the asthma problem. There is no doubt that asthma is often a reaction to stress and strain. The only difficulty is that the objective findings, particularly the chemical changes observed in asthma, are not always the same as those described by Selye for his adaptation syndrome. The problem is being studied further.

Williams<sup>72</sup> put forward the hypothesis that physical or intrinsic allergy (Menière's disease) is a disorder of the normal alarm reaction and that there is an inherited disorder of certain localized cells in which, in response to certain normal stimuli, the cells are unable to utilize the normal amount of adrenal hormones available to counteract the histamine released, or else too much histamine is released for the amount of available adrenal hormone to counteract.

\* \* \*

It will be noted that none of the investigations reviewed above have greatly helped an understanding of the fundamental basis of allergy. Most of the chemical changes observed in allergic disorders seem to be results of these conditions rather than causes of them.

The theory that treatment with potassium improves patients with allergic disorders has not been

generally accepted, and such therapy does not seem to be of great value. When disturbances of water balance occur, they should certainly be corrected. A study of the total balances, — that is, the total intake as compared to the total output, of sodium, potassium and water in the body, — together with the use of radioactive materials, may reveal more accurately than simple blood levels any shift of these substances in the cells and tissues of the body that may occur in allergy.

Therapy with calcium or magnesium is not specific for allergic conditions and is not indicated unless an actual deficiency of these substances in allergic patients is proved. So far as blood sugar is concerned, it would be interesting to know if it is at a low level at the onset of nocturnal attacks of asthma, if this can be shown, carbohydrate feedings before retiring at night may benefit some patients. Insulin shock seems to be justified only when psychiatric factors are dominant in aggravating the symptoms.

Since the metabolism of cholesterol and fat is not well understood in the normal person, it is hard to say whether a disturbance exists in allergic patients, although this does not seem likely on the evidence so far available.

Deficiencies of ascorbic acid or niacin cannot be incriminated as causative factors in allergy. There have been few reports on the functions of the other vitamins in allergic disorders, but from what is known about these vitamins at present it does not seem likely that any of them are specifically concerned. Perhaps a new vitamin will be discovered that may turn out to be of vital importance in allergy. Meanwhile, all patients suffering from chronic diseases should be properly fed, and the diet should include adequate amounts of all the known vitamins, with extra quantities if a deficiency exists.

Finally, few of the changes occurring in the body during the alarm reaction have been found in asthma. There have been no conclusive reports, however, on the blood chloride, on the blood globulin or on nitrogen metabolism in asthma. Studies of these factors ought to reveal whether or not asthma, eczema and kindred diseases belong with Selye's "diseases of adaptation." Studies of the function of the adrenal cortex in asthma are also needed.

From this review of investigations in chemical changes in allergy, it is obvious that in any future work strict attention must be given to exact methods, techniques and controls, since the status of asthma depends on many variable factors.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

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### CASE 33371

#### PRESENTATION OF CASE

*First admission.* A forty-three-year-old housewife entered the hospital because of generalized arthritis.

At the age of eighteen years the patient had had mild "rheumatism" in the legs, wrists and hands. Two years before entry the toes became swollen and painful, followed by similar involvement of the ankles and knees, the right knee more so than the left. The elbows, shoulders, jaws, hands and the spine then became affected at one time or another, and there had subsequently been a constant ache in the cervical spine. Occasionally, the joint symptoms were accompanied by fever. A year before entry the patient became unable to walk. She spent three months at a local hospital but obtained no relief, despite tonsillectomy and adenoidectomy. While she was there the eyes became red and lachrymose and began to ache. She could not read because of blurred vision. At the time of entry the hands, wrists and cervical spine were the source of the greatest discomfort. The aching pain was somewhat

relieved by aspirin. The patient had lost 18 pounds since the onset of the illness.

Physical examination revealed a pale, obese woman showing evidence of weight loss and moving with difficulty because of stiff joints. There were scattered telangiectases over the cheeks. The eyes showed lacrimation, photophobia, "bluish" scleras, moderately deep ciliary injection and many vitreous opacities. There were also some healing marginal infiltrates at the nasal border of the right cornea and several small, firm, gelatinous-appearing nodules in the conjunctiva of the left eye just above the insertion of the external rectus muscle. The fundi were normal so far as could be determined through the medial haze. The neck and spine were stiff. The lungs were clear. The heart was not enlarged to percussion. A harsh, low-pitched systolic murmur was heard over the entire precordium, loudest in the aortic area. The aortic second sound was absent. There was a moderate systolic blow at the apex. The abdomen was normal. The temporomandibular joints, shoulders, elbows, wrists, fingers, knees, ankles and toes were stiff and limited in motion, with enlargement, irregularity and tenderness. The fingers were tapering and spindle shaped. Scattered, small, tender subcutaneous nodules were found over the extremities, particularly at the elbows.

The temperature was 99.8°F, the pulse 105, and the respirations 22. The blood pressure was 140 systolic, 90 diastolic.

Examination of the blood disclosed a red-cell count of 4,340,000, with a hemoglobin of 70 per cent, and a white-cell count of 7800, with 95 per cent neutrophils. The total serum protein was 8.3 gm per 100 cc, with 4.0 gm of albumin and 4.3 gm of globulin. The sedimentation rate was 1.47 mm per minute. A blood Hinton test was negative.

A Congo-red test showed 100 per cent retention of the dye in the serum. The urinary sediment contained numerous white cells but was otherwise negative. A phenolsulfonephthalein test showed 50 per cent excretion of the dye in one hour.

On x-ray examination the heart was at the upper limits of normal. The lungs were clear. There was irregular destruction of the joint surface of the majority of the metacarpal, carpal, interphalangeal and phalangeal joints. The adjacent bone was markedly decalcified. No bony fusion was apparent, but there was slight subluxation in the first metacarpophalangeal joint. The feet showed similar changes. There were areas of subchondral destruction in the elbow and knee joints. The sacroiliac joints and spine disclosed no evidence of involvement. The sinuses were normal. There was marked callosities, with apical abscess formation about the first left lower molar and the first left upper molar bicusps. An electrocardiogram was normal.

The patient did well on aspirin, mild sedation, leg casts, raw liver and general supportive measures, with gradual simultaneous improvement in both joint and ocular symptoms. A biopsy of one of the subcutaneous nodules from the right elbow was reported as showing a "rheumatic nodule, probably rheumatoid." After three months in the hospital a definite soft aortic diastolic murmur appeared, and a low-pitched late diastolic rumble was thought to be present at the apex when the patient was lying on the left side.

Another electrocardiogram showed a greater shift to the left of the electrical axis than did the previous record. The sedimentation rate was 148 mm per minute. After four months in the hospital the patient was cystoscoped because of continued pyuria. Stones were found in the left ureter, and a left ureteromeatotomy was done to facilitate their passage. An intravenous pyelogram showed normal excretion of the dye bilaterally. On discharge after six and a half months in the hospital the patient had regained sufficient strength to walk 10 or 15 feet. At times she still had considerable pain in the knees and ankles. Objectively, the joints showed little change. The eyes were symptomatically improved, but the patient was unable to read because of the medial opacities.

*Final admission* (seven years later). After discharge the patient continued to feel much better, although the limitation of motion progressed slowly. Nevertheless, she was able to use a "walker" until one year before entry, when she had an acute exacerbation following a minor emotional upset (an altercation with a maid). Some months later several "abscessed" teeth fell out, and the right ear became painful, with perforation of the eardrum. At about the same time the ankles began to swell and five months before entry a physician noted an enlarged spleen and a slight amount of abdominal fluid. The edema and ascites gradually progressed. Three

paracenteses were performed, each productive of about 4000 cc of fluid.

Physical examination revealed massive edema from the feet to the lower chest. The pupils were slightly irregular, the right was larger than the left. Both nasal cavities were filled with dry bloody crusts. The lungs were clear, except for occasional rales at the bases. The border of the heart extended 13 cm to the left of the midsternal line in the fifth interspace. A harsh Grade III systolic murmur was heard over the entire precordium, but best over the midsternum in the third interspace. A Grade II, high-pitched diastolic murmur was loudest at the left sternal border in the third interspace. The spleen was ballotable five fingerbreadths below the costal margin. The liver edge was not felt, but by percussion it was two fingerbreadths below the costal margin. There was marked ascites. All the joints of the extremities showed progression of the arthritis, with marked limitation of motion and some subluxations.

The temperature was 99°F, the pulse 88, and the respirations 20. The blood pressure was 128 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 4,600,000, with 12.2 gm of hemoglobin, and a white-cell count of 4500, with 82 per cent neutrophils. The serum protein was 4.4 gm per 100 cc, with an albumin of 1.3 and a globulin of 3.2 gm. The nonprotein nitrogen was 79 mg, the serum cholesterol 250 mg and the cholesterol esters 178 mg per 100 cc. The corrected sedimentation rate was 185 mm per minute. A Congo-red test showed 46 per cent retention of the dye in the serum. The cephaloflucculation test was ++ in twenty-four and +++ in forty-eight hours. The thymol turbidity was 60 units. The urine was acid and had a specific gravity of 1.020. It gave a ++++ test for albumin. The sediment contained occasional hyaline casts and 15 to 20 white cells per high-power field.

An x-ray film of the chest revealed some prominence of the heart in the region of the left ventricle, with a cardiothoracic ratio of 16/31. There was a small amount of fluid in the right pleural sinus.

An electrocardiogram showed sinus rhythm. The rate was 75. The PR interval was 0.16 second, and the QRS complex 0.06. There were notched, low P waves and inverted T waves in Leads 1 and 2 and a flat T wave in Lead 3. The QRS complexes in Lead CF, were normal. The T wave in Lead CF, was inverted, and that in Lead CF, slightly inverted.

Despite the administration of Mercupurin, the patient excreted less than 500 cc. of urine a day. An abdominal paracentesis produced 4000 cc of cloudy-yellow fluid, with a specific gravity of 1.006. It contained many diplococci and 250 cells per cubic millimeter, 90 per cent of which were mononuclear forms. The patient gradually became hyperpneic,

lapsed into coma and died on the ninth hospital day

### DIFFERENTIAL DIAGNOSIS

DR ALFRED O LUDWIG There seems to be no doubt that this woman suffered from severe, progressive rheumatoid arthritis, which had persisted for a number of years, in fact since the age of eighteen. The particular points of interest in this case are the various complications that accompanied the disease. At the onset of the illness, the history indicated that she had the exacerbations and remissions that are common in rheumatoid arthritis in the early stages. Such episodes are frequent until the disease becomes chronic, on the other hand, it may become chronic from the start.

It is of particular interest that the patient had some lesions in the eyes. From the description given I suspect that these were due to episcleritis, which frequently occurs as a complication of rheumatoid arthritis. I believe that the pathologic picture was that of a rheumatoid nodule in this area. Another ocular complication of rheumatoid arthritis is iritis, of which there was no evidence in this case.

The physical examination at the first entry was characteristic of generalized and severe rheumatoid arthritis. It is interesting that at the examination on the first admission there was no aortic diastolic murmur — only a harsh, low-pitched, systolic murmur, which I am inclined to interpret as important clinically and about which I shall say more later.

Tender subcutaneous nodules are common in rheumatoid arthritis and occur most frequently over the elbows. They are similar to those found in rheumatic fever. They may also be found over the knees, over the lateral surfaces of the ulna and occasionally in other places. I believe that they are present in about 20 per cent of cases of rheumatoid arthritis. Their pathology differs somewhat from that seen in the nodules of rheumatic fever.

The temperature, pulse and respirations do not help us much. There was a slight degree of anemia at that time. It is significant that the total protein was increased to 8.3 gm per 100 cc, and that there was an increase of the globulin fraction to 4.3 gm. I might say here that hyperproteinemia and hyperglobulinemia are not unusual findings in rheumatoid arthritis. I cannot explain why this occurs. It bears some relation to the rapid sedimentation rate seen in certain cases, although it does not explain entirely the increased sedimentation rate. Occasionally, one sees the increased globulin reflected in the spinal fluid as well, and in such cases a strongly positive gold-sol curve of the paretic type may also be found. The blood Hinton and the spinal-fluid Wassermann reactions in such cases are negative. The total protein may also be increased in the spinal fluid as a reflection of this change in the blood. This is particularly important in patients in whom the

sacroiliac joints are involved, and such lesions may be confused with ruptured intervertebral disks.

At that time there was no abnormality in the Congo-red test. Whether or not the presence of white cells in the urine was significant, I do not know. We are not told whether this was a catheterized specimen. The phenolsulfonephthalein test was normal.

It is interesting that after three months of hospitalization a definite aortic diastolic murmur appeared. Someone thought that he heard a low-pitched, late, diastolic rumble at the apex, which suggests that there was definite valvular involvement of the heart, with lesions of the aortic and mitral valves. What does that mean in a case such as this? Here is a patient with apparently definite rheumatoid arthritis involving most of the joints who developed findings in the heart that are consistent with rheumatic heart disease, or at least are those that one usually associates with it. A number of cases have been described in which heart lesions of this sort occurred coincident with chronic rheumatoid arthritis.\* These lesions are predominantly located on the aortic valves. We also have seen such cases in this hospital. I do not know whether or not the histology of this type of endocarditis differs from that found in rheumatic fever.

It is also interesting that the electrocardiogram showed a greater left-axis deviation than previously. The sedimentation rate, of course, was greatly elevated, the normal being 0.35 mm per minute.

It was thought necessary to cystoscope this patient because of continued pyuria. Apparently, the white cells previously reported in the urine were important. Stones were found on that examination, which raises the question how the stones got into the left ureter. Two possibilities suggest themselves. In the first place, this patient, like all patients with severe chronic rheumatoid arthritis, had a great deal of decalcification and, therefore, undoubtedly excreted much more calcium in the urine than normally. Furthermore, she had a urinary infection. Whether the infection preceded and therefore contributed to the stones or whether it followed the stones, I do not know. At that time she still did not show any decrease in renal function. It is obvious that she had not really made any great clinical progress after the long period of hospitalization.

At the second admission the important points were the appearance of edema of the ankles, an enlarged spleen and the presence of abdominal fluid. From that time on, both edema and ascites increased steadily to the point where three abdominal paracenteses had to be done. Examination confirmed this finding of massive edema from the chest down. I cannot believe that the irregularity of the pupil

\*Baggenstoss, A. H., and Rosenberg, E. F. Cardiac lesions associated with chronic infectious arthritis. *Arch Int Med* 67:241-258, 1941.

was important, except that it may have been evidence of a previous intus. The heart border extended 13 cm. to the left. That is significant, but one cannot be certain that the enlargement was not apparent and due to increased abdominal fluid, which pushed the heart up and out. The murmurs had definitely changed. There was a Grade III systolic murmur over the precordium, heard best over the mediastinum, and a Grade II, high-pitched aortic diastolic murmur, loudest at the left sternal border, the position in which one usually expects to hear aortic murmurs best. Both the spleen and the liver appeared to be considerably enlarged. The joint lesions had shown continued progression.

The laboratory findings are of some importance. There was still a slight degree of anemia. This and the diminution of the white-cell count occur in rheumatoid arthritis. The leukopenia was part of what has been described as Feltz's syndrome—a clinical picture consisting of leukopenia, splenomegaly and lymphadenopathy in association with rheumatoid arthritis. The serum protein was below normal, but there was still a marked increase in the amount of globulin, with reversal of the albumin-globulin ratio. The nonprotein nitrogen was elevated to more than twice the normal, and there was also an increase in the cholesterol and cholesterol esters. The sedimentation rate was as high as before. I do not believe that the Congo-red test was significant. The cephalin-flocculation and the thymol-turbidity tests, as well as the increased globulin level in the serum, are used to aid in the diagnosis of decreased liver function. The urinary findings improved. There was marked albuminuria, with presumably a good specific gravity—if the patient could concentrate to 1 020, she had not lost much renal function.

I shall have to ask a cardiologist to interpret the electrocardiogram.

The final course showed increasing oliguria. Abdominal paracenteses continued to produce large amounts of fluid. We are told that the fluid became infected. Diplococci and leukocytes were found in it, so that the patient was developing or had already developed a low-grade peritonitis, presumably due to a pneumococcus. This is not infrequent with nephrosis and is not rare as the terminal event with this complication. The hyperpnea I explain on the basis of acidosis from increasing renal failure.

There are several perplexing points about the case. What other possibilities might account for these complications? We have a good deal of evidence that this patient had rather extensive amyloid infiltration, including an amyloid nephrosis. The renal findings were consistent with it, as was the Congo-red test and the enlargement of the liver and spleen. There are other things, however, that may have been implicated. The patient may have had a sufficient degree of impaired liver function with cirrhosis to account for the ascites, although I

do not believe from the information at hand that one is justified in drawing that conclusion.

Finally, is it necessary to assume any serious degree of heart failure to account for the production of ascites? I do not believe from the clinical findings that this is so. Nor is there sufficient evidence to say that there was impairment of the venous return to the heart. One might consider a tricuspid lesion, of which I cannot see any evidence. So far as the kidneys are concerned, one cannot forget that the patient had renal infection, pyelitis and pyelonephritis, which may also have contributed to the eventual breakdown of renal function. Before we go farther, it would be wise to see if the x-ray film will help and also to ask the cardiologists to interpret the electrocardiographic findings.

DR STANLEY M. WYMAN Unfortunately, the films of the first examination are no longer available. This film of the chest was taken in the supine position, so that accurate measurement of the heart is impossible. The right leaf of the diaphragm is elevated more than usual. The lung fields are clear. The heart shadow may be prominent toward the left. The changes in the hand are those of severe osteoporosis, with loss of subchondral bone in the carpal bones and in the terminal portions of several of the phalanges.

DR LUDWIG These x-ray films show extensive destruction around the joints.

DR EDWARD F. BLAND The electrocardiogram shows a digitalis effect on the ST intervals and perhaps evidence of slight left ventricular strain.

DR LUDWIG I should be satisfied to leave the diagnosis as extensive, severe chronic rheumatoid arthritis complicated by serositis and by a heart lesion, the nature of which I am not certain. I think it will be demonstrated that there was involvement of both the aortic and the mitral valves and, finally, that there was extensive amyloid infiltration secondary to the rheumatoid arthritis and involving primarily the spleen, liver and kidneys. I also predict that there was some degree of pyelonephritis.

DR BLAND We saw this patient repeatedly in 1939 and 1940. We were especially interested at that time in a group of patients with rheumatoid arthritis who also had valvular heart disease. One of this group had a high degree of nonspecific aortitis and aortic regurgitation, which Dr. Mallory was not quite willing to classify at autopsy. This patient, however, does not seem to fit this special group. The cardiac signs began with a systolic murmur, and it was not until considerably later that we also recognized an aortic diastolic murmur. Aortic-valve disease, with predominant stenosis acquired at a relatively early age, always suggests the possibility that an inflammatory lesion has been superimposed on a bicuspid aortic valve. I should like to throw that possibility in. I doubt if she had mitral disease except on a statistical basis.

DR LUDWIG On the basis of the type of heart disease that we see in rheumatoid arthritis?



lapsed into coma and died on the ninth hospital day

### DIFFERENTIAL DIAGNOSIS

DR ALFRED O LUDWIG There seems to be no doubt that this woman suffered from severe, progressive rheumatoid arthritis, which had persisted for a number of years, in fact since the age of eighteen. The particular points of interest in this case are the various complications that accompanied the disease. At the onset of the illness, the history indicated that she had the exacerbations and remissions that are common in rheumatoid arthritis in the early stages. Such episodes are frequent until the disease becomes chronic, on the other hand, it may become chronic from the start.

It is of particular interest that the patient had some lesions in the eyes. From the description given I suspect that these were due to episcleritis, which frequently occurs as a complication of rheumatoid arthritis. I believe that the pathologic picture was that of a rheumatoid nodule in this area. Another ocular complication of rheumatoid arthritis is iritis, of which there was no evidence in this case.

The physical examination at the first entry was characteristic of generalized and severe rheumatoid arthritis. It is interesting that at the examination on the first admission there was no aortic diastolic murmur—only a harsh, low-pitched, systolic murmur, which I am inclined to interpret as important clinically and about which I shall say more later.

Tender subcutaneous nodules are common in rheumatoid arthritis and occur most frequently over the elbows. They are similar to those found in rheumatic fever. They may also be found over the knees, over the lateral surfaces of the ulna and occasionally in other places. I believe that they are present in about 20 per cent of cases of rheumatoid arthritis. Their pathology differs somewhat from that seen in the nodules of rheumatic fever.

The temperature, pulse and respirations do not help us much. There was a slight degree of anemia at that time. It is significant that the total protein was increased to 8.3 gm per 100 cc, and that there was an increase of the globulin fraction to 4.3 gm. I might say here that hyperproteinemia and hyperglobulinemia are not unusual findings in rheumatoid arthritis. I cannot explain why this occurs. It bears some relation to the rapid sedimentation rate seen in certain cases, although it does not explain entirely the increased sedimentation rate. Occasionally, one sees the increased globulin reflected in the spinal fluid as well, and in such cases a strongly positive gold-sol curve of the paretic type may also be found. The blood Hinton and the spinal-fluid Wassermann reactions in such cases are negative. The total protein may also be increased in the spinal fluid as a reflection of this change in the blood. This is particularly important in patients in whom the

sacroiliac joints are involved, and such lesions may be confused with ruptured intervertebral disks.

At that time there was no abnormality in the Congo-red test. Whether or not the presence of white cells in the urine was significant, I do not know. We are not told whether this was a catheterized specimen. The phenolsulfonephthalein test was normal.

It is interesting that after three months of hospitalization a definite aortic diastolic murmur appeared. Someone thought that he heard a low pitched, late, diastolic rumble at the apex, which suggests that there was definite valvular involvement of the heart, with lesions of the aortic and mitral valves. What does that mean in a case such as this? Here is a patient with apparently definite rheumatoid arthritis involving most of the joints who developed findings in the heart that are consistent with rheumatic heart disease, or at least are those that one usually associates with it. A number of cases have been described in which heart lesions of this sort occurred coincident with chronic rheumatoid arthritis.\* These lesions are predominantly located on the aortic valves. We also have seen such cases in this hospital. I do not know whether or not the histology of this type of endocarditis differs from that found in rheumatic fever.

It is also interesting that the electrocardiogram showed a greater left-axis deviation than previously. The sedimentation rate, of course, was greatly elevated, the normal being 0.35 mm per minute.

It was thought necessary to cystoscope this patient because of continued pyuria. Apparently, the white cells previously reported in the urine were important. Stones were found on that examination, which raises the question how the stones got into the left ureter. Two possibilities suggest themselves. In the first place, this patient, like all patients with severe chronic rheumatoid arthritis, had a great deal of decalcification and, therefore, undoubtedly excreted much more calcium in the urine than normally. Furthermore, she had a urinary infection. Whether the infection preceded and therefore contributed to the stones or whether it followed the stones, I do not know. At that time she still did not show any decrease in renal function. It is obvious that she had not really made any great clinical progress after the long period of hospitalization.

At the second admission the important points were the appearance of edema of the ankles, an enlarged spleen and the presence of abdominal fluid. From that time on, both edema and ascites increased steadily to the point where three abdominal paracenteses had to be done. Examination confirmed this finding of massive edema from the chest down. I cannot believe that the irregularity of the pupil

\*Baggenstoss, A. H., and Rosenberg, E. F. Cardiac lesions associated with chronic infectious arthritis. *Arch. Int. Med.* 67: 241-258, 1941.

brought to a steady level of 123 to 143 mg. The hemoglobin, white-cell count, differential count, serum nonprotein nitrogen, total protein and carbon dioxide were within normal limits. Repeated sputum examinations were negative for tubercle bacilli. A chest film revealed an area of increased density extending upward from the left lung root into the apical division of the left upper lobe. There was a 5-cm., ragged cavity within it that seemed to have a fluid level. The left leaf of the diaphragm was elevated but moved freely. There was a small amount of fluid in the left pleural sinus. The left upper lobe was not much reduced in size. The right lung was clear. Two bronchoscopic examinations disclosed constriction of the left upper-lobe bronchus, but both biopsies and smears were negative for carcinoma.

The patient was discharged on the eighteenth day.

*Second admission* (one month later). The patient was readmitted with fever, chills and dyspnea. In the interval he had felt reasonably well except for persistent cough and expectoration of about a cupful of sputum a day, which was blood streaked on occasions. He continued to have pain off and on in the left anterior portion of the chest, along with some substernal pressure, but this was not related to exercise, cough or deep respiration. There was no appreciable weight loss. One day before admission he had dyspnea, chills and fever.

Physical examination showed no change from those on the first admission.

The temperature was 103°F, the pulse 100 and the respirations 23, but these were readily controlled with penicillin therapy.

Examination of the blood revealed a white-cell count that varied from 14,800 to 10,000. The fasting blood sugar was 121 to 139 mg per 100 cc. The blood chemical findings were otherwise normal.

X-ray examination showed some increase in the size of the cavity in the left upper lobe and some elevation of the left leaf of the diaphragm.

A third bronchoscopy showed only constriction of the left upper-lobe bronchus, the biopsy was negative for carcinoma.

An operation was performed on the twenty-third hospital day.

#### DIFFERENTIAL DIAGNOSIS

Dr. LOWREY F. DAVENPORT. Since most of the findings, including the sputum examination and bronchoscopy, were negative, our chief reliance is on the serial x-ray films, and I should like to request that they be shown.

Dr. STANLEY M. WYMAN. The cavity discussed lies in the apex of the left upper lobe medially. It can be distinctly seen in the lateral view. There is some density throughout the apical portion of the left upper lobe. Elevation of the left leaf of the diaphragm is well seen in the entire series. A film taken twelve days later shows a definite fluid level

in the base of the cavity, but no other essential change. In a film taken a month later the cavity appears to be considerably larger, with again a small fluid level in its base. A film taken two weeks later shows no definite change except for some decrease in the reaction around the ring shadow. There is, however, one thing to add to this report — that is, what appears to be a small nodule in the right lower-lung field. This is present only on the film taken at the last examination.

Dr. DAVENPORT. Two months prior to the first admission this fifty-six-year-old man presented symptoms of a respiratory infection — fever, cough and sputum. The subsequent course on the two hospital admissions and the serial x-ray films suggest a destructive process involving the left upper lobe. We are faced, as we always are in these cases, with the problem of trying to differentiate simple lung abscess and abscess complicated by tumor or some chronic type of inflammatory process, such as tuberculosis. I believe that it is to these three possibilities only that we should give our serious attention.

Confusing things about symptomatology often arise now that the antibiotics, such as penicillin, have become available. We have often been misled by the thought that a definite — sometimes a dramatic — response in temperature, white-cell count and the site of the x-ray shadow following penicillin are evidence against the possibility of an underlying tumor. We should remember that if there is bronchial obstruction with underlying suppuration the inflammatory reaction secondary to the bronchial obstruction can be influenced markedly by penicillin and the various sulfonamides. The facts that the original episode of so-called "grippe" responded to treatment and that the symptoms of inflammation at the time of the first admission responded to penicillin therapy are of no help in reassuring us regarding the inflammatory nature of the process.

Always, when a patient presents glycosuria, as in the case under discussion, and an elevated blood sugar, we must be on the lookout for the bizarre forms of tuberculosis. Tuberculosis in a diabetic patient is notoriously difficult to diagnose in some of the early stages because it does not behave according to the usual pattern. It starts out with a fulminating process, with inflammation and an acute exudative process similar to acute lobar pneumonia, and may excavate readily. But in a patient in the hospital for as long a period as this patient was, with repeated sputum examinations and a cavity as large as this, in whom no tubercle bacilli have been found in repeated searches, it is reasonable to exclude tuberculosis. Occasionally in tuberculosis sanatoriums we see cavities with negative sputum on persistent examination. Most of them are observed in cases of chronic productive tuberculosis in which the cavity has epithelialized. I cannot conceive of tuberculosis in such a rapidly destruc-

tive process as this without innumerable tubercle bacilli in the sputum

Could this have been a simple lung abscess that had been held more or less in abeyance by sulfonamide therapy and antibiotics? There are several points in the history against the possibility that this was the type of abscess that follows tooth extraction, foreign body or toxemia. The rapidity of excavation and the type of sputum were much against it. Also, bronchoscopy gave chiefly negative evidence but one bit of helpful data although there was no evidence of growth in the bronchus, constriction of the left upper-lobe bronchus was noted on both occasions. If this had been tuberculosis of a rapid fulminating nature, constriction on a tuberculous basis could not have taken place so quickly. Nor, in simple lung abscess, would one expect constriction, even though the bronchoscopic findings were essentially negative.

The report on two occasions that there was constriction of the bronchus in the left upper lobe makes me lean definitely to the diagnosis of primary bronchiogenic cancer, with bronchial obstruction, suppuration and excavation. That brings us up to the method of handling these cases. Before the days of chemotherapy when the chest was opened with fear, and before pneumonectomy and lobectomy were being done, we studied some of these patients overzealously, trying to establish the diagnosis between a simple lung abscess, tumor and inflammatory, nontuberculous and tuberculous processes. We now believe that it is wise to excise a localized destructive process in the lung, whether benign or malignant, suppurative or tuberculous, in the absence of definite evidence of involvement elsewhere. As is well known, more and more frequently we are going ahead in cases of localized tuberculosis and picking primary resection as the treatment of choice. Since I have seen these x-ray films and had the nodule called to my attention, I am somewhat more hesitant about recommending operation because I lean strongly to a malignant process, and if this was a malignant process, with a metastatic nodule already formed at the right base, operation, of course, was hopeless from the standpoint of effecting a cure. This nodule also raises the bare possibility that the left upper-lobe process was

not a primary bronchiogenic carcinoma but a metastatic process. I think that that is most unlikely because metastatic nodules rarely cause obstruction and ordinarily do not break down and excavate as the lesion did in this case.

I should have advised operation on the first admission with the tentative working diagnosis of primary bronchiogenic cancer, with secondary excavation due to a blocking process and suppuration.

#### CLINICAL DIAGNOSIS

Lung abscess (? carcinoma)

DR DAVENPORT'S DIAGNOSIS

Carcinoma of lung

#### ANATOMICAL DIAGNOSIS

*Squamous-cell carcinoma of lung*

#### PATHOLOGICAL DISCUSSION

DR LAMAR SOUTTER. When the chest was entered, innumerable dense adhesions were found over the entire lung. These were freed, and the abscess entered at the apex of the lung, where it was adherent to the upper part of the chest anteriorly. The abscess extended down along the mediastinal vessels and the arch of the aorta into the posterior portion of the chest. The septum between the upper and lower lobes could not be dissected clear because the abscess extended across it. It was obvious that a pneumonectomy would be necessary. Because of the extensive infection along the mediastinum and the large hilar nodes, it was thought that this procedure would be very hazardous, hence, the chest was closed. A catheter was inserted for drainage.

DR BENJAMIN CASTLEMAN. A biopsy of the abscess wall showed a well differentiated squamous-cell carcinoma, with marked epithelial pearls and keratinization. This abscess was broken-down tumor rather than a true non-neoplastic abscess beyond an obstructing tumor, which not infrequently occurs in the lung. In this latter group of cases we have seen metastatic cerebral abscesses without metastases from the cancer itself.

A PHYSICIAN. What was the eventual course?

DR CASTLEMAN. The patient is still on the ward and receiving x-ray treatment. It is planned to achieve a total dosage of 3000r.

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## TETANUS IN THE UNITED STATES ARMY IN WORLD WAR II

EARLY last year Boyd<sup>1</sup> reviewed the British experiences with tetanus in the African and European theaters of operation, and his report has already been commented on in these columns.<sup>2</sup> Active immunization as employed at first in the British Army consisted of two doses of toxoid, 1 cc each, about six weeks apart. Later a third dose was included in the initial course. An annual booster dose of 1 cc was also given, and in addition, a single dose of 3000 units of tetanus antitoxin was administered immediately after a wound was sustained in those who had been actively immunized. The same amount of antitoxin was given at weekly intervals to those who had not been immunized. Boyd concluded from his data that tetanus

was not entirely prevented by active immunization, since 22 cases occurred in persons who had been actively immunized. Furthermore, although the mortality from the disease was significantly lower in those actively immunized patients who had also received prophylactic antitoxin, in patients who were actively immunized and had not received antitoxin the mortality was not below average. He therefore concluded that the failures were due to a low level of antitoxin at the time of wounding and that this was best remedied by giving antitoxin during the period while the patient was making his own, the best effects being obtained from the early administration of antitoxin.

Corresponding data from the United States Army are now available and are of particular interest because of the differences in the methods employed and in the results attained.<sup>3</sup> In the Army, fluid, not alum-precipitated, tetanus toxoid has been used as an immunizing agent for the prevention of tetanus since 1941. All military personnel received a series of three subcutaneous injections of 1 cc at intervals of three weeks. A routine stimulating injection of 1 cc of toxoid was administered one year after the initial series, and an emergency stimulating dose was given on the incurrence of wounds, severe burns or other injuries that might result in tetanus. In addition, a stimulating dose was also given at the time of manipulation of old wounds that were considered as potentially contaminated by *Clostridium tetani*. Before September, 1944, an additional stimulating dose of 1 cc was given to all persons departing for a theater of operations more than six months after the basic series or the routine stimulating dose, after that time data indicating that this precaution was not necessary had accumulated. At present no further toxoid is given after the routine stimulating dose unless the individual sustains an injury that might result in tetanus, at which time the emergency stimulating dose of 1 cc of toxoid is administered. Tetanus antitoxin is reserved for the treatment of clinical tetanus and for passive immunization of injured persons in whom there is no evidence of previous administration of toxoid.

Studies were made to determine the levels of antitoxin during the various stages in these im-

munization procedures. It was found that one week after the third injection of the initial series, all specimens contained at least 0.1 unit of antitoxin per cubic centimeter of serum and some contained much more. Since the amount of circulating antitoxin required for protection against tetanus is estimated to be between 0.01 and 0.20 unit per cubic centimeter of serum, it was considered that there was adequate protection immediately after completion of the initial series and that there was no need for prophylactic antitoxin. To determine how long a basic active immunity persists that is sufficient to allow for adequate response to a stimulating dose, a group of persons was studied one year after the completion of the basic course of toxoid. Before administration of the stimulating dose relatively small quantities of circulating antitoxin were present, but one week after this stimulating dose, levels of 0.3 unit or more per cubic centimeter were reached in almost every subject. Comparable results had previously been obtained by Mueller and his associates.<sup>4</sup> In immunized persons who had not received injections of toxoid over a period of from two to five years, only about 10 per cent failed to develop a level of antitoxin that was adequate for protection and the protective levels were produced within a week in all cases. It was therefore considered wise to continue the administration of emergency stimulating doses of toxoid following injury, and it was also thought that an adequate response would then occur within the usual incubation period of tetanus.

Two types of reactions to the toxoid were observed. The first was apparently nonspecific in nature and was manifested by symptoms similar to those that occur after typhoid vaccination, that is, local soreness at the site of injection, headache, general malaise and occasionally chills and fever. These local and general reactions were much less frequent and less severe than those following the injection of typhoid vaccine. The second type of reaction was characterized by the appearance—within thirty minutes—of flushing and itching of the skin or of frank urticaria and occasionally edema of the lips and eyelids. Edema of the glottis and respiratory difficulties were rare. In about 85 per cent of the cases these reactions occurred after the

second or third dose, suggesting the production of a hypersensitive state by a previous dose. The majority of the latter type of reactions occurred in the tetanus immunization program, and it was soon recognized that they were a manifestation of sensitivity to some constituent of the toxoid that toxoids containing certain types of peptones were the worst offenders. Cessation of the use of toxoids containing these peptones was followed by a decrease in the frequency of these reactions from 63 per 100,000 injections to less than 2. The incidence of reactions resulting from the use of toxoids now available is extremely low, and reactions from initial injections of these materials are almost nonexistent.

Throughout the entire war period only 12 cases of tetanus occurred among Army personnel, although some other cases may have been overlooked. It also occurred among wounded soldiers who fell into the hands of the enemy. The 12 recognized cases included 4 that resulted from injuries sustained while on active duty. Interestingly enough, only 6 of the 12 cases occurred in those who had received full prophylactic doses, including the emergency stimulating dose of toxoid after injury.

A comparison with the previous experience in the Army is of interest. In World War I, there were 70 cases of tetanus among approximately 10 million admissions for wounds and injuries, an incidence of 13.4 per 100,000. In the period between the two world wars there was a similar total number of admissions, with 14 cases of tetanus or 2.4 per 100,000. In World War II there were about three million admissions for wounds and injuries with a tetanus case rate of only 0.44 per 100. Furthermore, a considerable number of cases of serum sickness were undoubtedly prevented thereby the avoidance of prophylactic antitoxin in the latter period.

The incidence among enemy forces is not entirely known, but from the data that are available American experience stands out most favorably. For example, it has been reported that there were some 10 cases per 100,000 wounded in the Japanese Army and Navy from 1940 through 1944, a rate comparable with that which occurred among American troops in World War I. Among civilians

casualties during the Manila operations there were almost 500 cases. A report from Europe states that during the Normandy invasion unimmunized German ground forces suffered over 80 cases of tetanus but that there were no such cases in the immunized *Luftwaffe*. There were also 53 cases among American-held German prisoners of war in England during a single month in the latter part of 1944.

The Army report also reviews the civilian mortality from tetanus in the United States and draws attention to the high mortality rate, especially during infancy and early childhood. The civilian mortality rate in young adults during the period of 1936-1938 was calculated as being about twenty times as high as the Army rate in World War II.

From experience gained in the use of tetanus toxoid in the war there is no doubt regarding the efficacy of this procedure for the prevention of tetanus. In military practice reliance was not placed on a continuing state of immunity following immunization, instead, advantage was taken of the rapid rise in blood antitoxin levels that occurs soon after the administration of a stimulating dose of toxoid. Although tetanus is not frequently encountered in civilian practice, it is sufficiently important to warrant active immunization of children and of adults whose activities might lead to injuries potentially infected with *Cl. tetani*. Such persons, when immunized, should be furnished with a record of the procedure so that physicians subsequently treating their injuries may know that the administration of toxoid and not of antitoxin is the treatment of choice.

The Army experience gives no indication concerning the relative efficacy of alum-precipitated toxoid. For children, that agent is thought to be quite satisfactory, particularly since it lends itself well to combination with other antigens, such as diphtheria toxoid. Fluid toxoid, because of its more rapid absorption is considered to be the agent of choice for the booster dose, but there is no good indication that the alum-precipitated material is not just as effective under these circumstances.

In general, it is probably a reasonably safe procedure to give toxoid rather than antitoxin prophylactically to an ex-serviceman who sustains an injury if he states that he was in service for at least a year

subsequent to Pearl Harbor and that he received all the routine immunizations administered in his organization. Such a military experience would almost certainly indicate that he had received at least the basic course and would therefore be expected to respond satisfactorily to a stimulating dose of tetanus toxoid.

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#### GREATER BOSTON NURSING COUNCIL

THERE has been a succession of birthday observances over the years—tercentenaries, sesquicentennials and centenaries—as the settlements and the institutions of our country have paused at various chronologic vantage points to view the achievements of their past. A local youngster now calls attention to the accomplishments of its first decade of life.

The Greater Boston Nursing Council, although organized as the Community Nursing Council on November 17, 1937, had its actual beginning seventeen years earlier in the Committee on Public Health Nursing of the Boston Health League—that uncannily ubiquitous and inclusive organization that, like the news weekly, sees all and hears all. Interested in being sure that all groups in the community had adequate nursing care, the Committee on Public Health Nursing appointed a committee to ascertain the nursing needs in Boston and the community resources to meet these needs. As a result of the recommendations of this committee the Community Nursing Council came into being, becoming in 1942 the Greater Boston Nursing Council for War Service and in 1946 simply the Greater Boston Nursing Council, under which name it now functions.

The activities and the accomplishments of the Nursing Council have already been many as it arrives at its tenth birthday. In the legislative field, with the Massachusetts State Nurses Association, it has been active in promoting legislation to

make mandatory the registration of nurses and to regulate subsidiary workers In 1942 and 1943 it recruited graduate nurses for the staffing of the proposed Army hotel hospitals, which fortunately were not needed, it did the important work of classifying nurses under the Procurement and Assignment Service of the War Manpower Commission For nearly five years it has been active in recruiting students for the Greater Boston nursing schools It has undertaken a number of surveys of nursing services, it has studied nurses' salaries, it is currently sponsoring a committee to consider the matter of experience and observation in public-health nursing for graduate and undergraduate students

The Nursing Council will continue to have ample opportunity to make its services felt, for the difficulties of supply and demand and the costs in the nursing field continue in an acute phase We are fortunate in having such an organization ready to do its share in the study of these problems

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1947

RÉSUMÉ			
DISEASES	JULY 1947	JULY 1946	SEVEN YEAR MEDIAN
Chancroid	2	2	2*
Chicken pox	664	516	436
Diphtheria	20	31	13
Dog bite	1348	1333	1229
Dysentery, bacillary	11	5	23
German measles	52	133	116
Gonorrhea	352	447	356
Granuloma inguinale	—	1	1*
Lymphogranuloma venereum	—	2	3*
Malaria	15	39	12
Measles	616	2534	1420
Meningitis, meningococcal	8	4	13
Meningitis, Pfeiffer bacillus	1	2	2
Meningitis, pneumococcal	2	6	3†
Meningitis, staphylococcal	—	—	0†
Meningitis, streptococcal	—	—	0†
Meningitis, other forms	—	—	0†
Meningitis, undetermined	3	8	5†
Mumps	346	216	434
Pneumonia, lobar	107	70	100
Poliomyelitis	21	11	9
Salmonellosis	13	16	11
Scarlet fever	122	179	241
Syphilis	216	486	388
Tuberculosis, pulmonary	251	256	235
Tuberculosis, other forms	13	13	17
Typhoid fever	1	7	4
Undulant fever	6	11	4
Whooping cough	551	562	562
*Three-year median			
†Five-year median			

COMMENT

Diseases above the seven-year median were chicken pox, diphtheria, dog bite, malaria, lobar pneumonia, poliomyelitis, salmonellosis and undulant fever Chicken pox was at the highest level in the records of the Department. Diphtheria declined again, there were 20 cases in July compared with 38 and 37 for May and June, respectively

Poliomyelitis showed the usual seasonal increase, with 21 cases in July whereas only 9 were reported for the preceding six months, 11 were reported in July, 1946 Diseases below the seven-year median were bacillary dysentery, German measles, gonorrhea, measles, meningococcal and Pfeiffer bacillus meningitis, mumps, scarlet fever, syphilis, tuberculosis, typhoid fever and whooping cough. Measles reached the lowest level since 1935, and scarlet fever the lowest in the records of the Department

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Billerica, 1, Boston, 10; Chelsea, 1, Duxbury, 1, Foxboro, 1, Lynn, 1, Revere, 1, Somerville, 1, Winchendon, 1, total, 20  
Dysentery, bacillary, was reported from Worcester (State Hospital), 11, total, 11  
Encephalitis, infectious, was reported from Dover, 1, total, 1  
Lymphocytic choriomeningitis was reported from Quincy, 1, total, 1  
Malaria was reported from Barnstable, 1, Boston, 3, Cambridge, 1, Everett, 1, Greenfield, 1, Holbrook, 1, Lynn, 1, Nantucket, 1, New Bedford, 1, North Andover, 1, Waltham, 1, Williamstown, 1, Worcester, 1, total, 15  
Meningitis, meningococcal, was reported from Boston, 2, Framingham, 1, Lowell, 1, Malden, 1, Montague, 1, Quincy, 1, Waltham, 1, total, 8  
Meningitis, Pfeiffer bacillus, was reported from West Springfield, 1, total, 1  
Meningitis, pneumococcal, was reported from Cambridge, 1, Leominster, 1, total, 2  
Meningitis, undetermined, was reported from Norwood, 1, Taunton, 1, Ware, 1, total, 3  
Rocky Mountain spotted fever was reported from Chatham, 1, Dennis, 1, Worcester, 1, total, 3  
Salmonellosis was reported from Boston, 3, Cambridge, Lawrence, 2, Waltham, 1, Wellesley, 1, Worcester, total, 13  
Septic sore throat was reported from Boston, 1, Nor Brookfield, 2, total, 3  
Tetanus was reported from Acton, 1, Attleboro, 1, Hopkinton, 1, Pittsfield, 1, total, 4  
Trichinosis was reported from Adams, 1, Boston, Fitchburg, 3, total, 5  
Tularemia was reported from Bourne, 2, total, 2  
Typhoid fever was reported from Somerset, 1, total, 1  
Undulant fever was reported from Ashburnham, Bolton, 1, Holbrook, 1, Warren, 1, Worcester, 2, total, 6

MISCELLANY

BOSTON UNIVERSITY APPOINTMENTS

Dr Jacob W Stutzman, a member of the department physiology at the University of Wisconsin and for the two years assistant professor of physiology at that institution, has been appointed associate professor of pharmacology at Boston University School of Medicine  
Dr Sidney Licht, chief of medical rehabilitation and physical medicine for the Veterans Administration in New England, has been appointed a lecturer in physical medicine at Boston University School of Medicine Dr Licht, a resident of Cambridge, formerly taught at Columbia University at New York University

CORRESPONDENCE

VACCINATION AGAINST RUBELLA

To the Editor I have read the comprehensive and critical review of rubella by Dr Wesselhoeft, which appeared in June 19 and 26 issues of the Journal, with great interest The recent knowledge of the serious effect on the fetus of this disease is contracted by the mother early in pregnancy poses new and serious problems from the viewpoint of the health officer Dr Wesselhoeft ably discusses the problems of prevention and discards as potentially too dangerous any plan to relax further our isolation practices or to

late children with rubella virus at an appropriate age. It is my conviction that the practice of inoculation presents less danger of infection of pregnant mothers than the risk that they now run of contracting the disease from contact with unknown and unsuspected cases during epidemics.

German measles is in its own right perhaps the mildest of the acute epidemic diseases and complications as Dr Wesselhoft asserts, are rare. Assuming that techniques of artificial inoculation can be worked out to reproduce the disease in its natural or even a milder form the danger to the child will be no greater than the present risk or even than the present practice of vaccination against smallpox. Inoculation could be limited to girls but might better include all children. The time and conditions under which the child would be given rubella in private practice could be selected with regard to the known absence of pregnancy in the mother of the family. With pre-school children knowing the incubation period and the duration of the communicable state isolation would be relatively easy and reliable. The argument that immunity is not always permanent is valid but experience shows that second attacks are extremely rare. This practice would protect the next and succeeding generations from the occasional, but dreadful tragedy of infecting on their unborn offspring the infirmities of prenatal rubella as well as saving the mother from the risk of miscarriage.

The proposed program cannot be approached lightly or launched without most careful consideration of all possible contingencies. Our knowledge of artificial inoculation is meager. It should be experimented with under carefully controlled conditions in institutions to learn the best means of introducing the virus, the time and duration of the period of communicability and other pertinent details.

Whether adolescent and adult women who have no known history of rubella might be safely inoculated is another question that deserves consideration. With absolute knowledge of the fact that pregnancy does not exist the proposal does not seem unreasonable.

Although mumps presents an entirely different problem it may be worthwhile in passing to propose that we encourage exposure of young children to this disease or practice artificial inoculation. Its consequences in preadolescents are practically nil and complications are exceedingly rare whereas later in life orchitis in the male may be a serious affair.

I realize that the above proposals are radical and unconventional. As one who has spent much of his life in teaching and in practicing as a health officer the prevention of epidemic diseases it may seem literal heresy. Yet I have observed the futility of our best efforts in attempting to control the acute epidemic diseases of childhood by isolation and quarantine alone. Rubella outbreaks appear spread and run their course in spite of our efforts. Now that we are confronted with a hitherto unsuspected danger to life and health from this disease, even if only rarely when we have the simultaneous occurrence of early pregnancy and rubella. I believe that the public health profession should study every possibility to prevent this event. The above proposal is at least worth further study and consideration.

C. M. HILLIARD

Simmons College  
Boston

Professor Hilliard's letter was referred to Dr Wesselhoft, whose reply is as follows:

To the Editor. The suggestion contained in Professor Hilliard's communication is a commendation devoutly to be wished but there are difficulties in bringing it about which were presented in my progress review on rubella. It is not an easy matter to cultivate the virus of rubella and furthermore, the inoculation of such material does not ensure a successful take. Until a more successful method of cultivation of the virus is achieved than has been accomplished up to the present, inoculation cannot be considered a practical procedure.

I am heartily in agreement with Professor Hilliard that every effort should be made to perfect a satisfactory vaccine against rubella. Without such a vaccine, it is well to keep in mind the problems that I attempted to set forth under the heading "Prevention."

CONRAD WESSELHOFT, M.D.

315 Marlboro Street  
Boston

## BOOK REVIEWS

*Treponematoses*. By Ellis Herndon Hudson. 4° paper, 122 pp. New York: Oxford University Press, 1946. Reprinted from *Oxford Medicine*.

This book constitutes a new and important interpretation of available evidence regarding the relation between the various maladies produced by treponemes. The evidence considered embraces the historical, clinical, pathological, immunologic and epidemiologic aspects of the question. The facts have been marshaled logically and presented clearly and unemotionally.

The essential conclusions are that at present, there is no justification for regarding *Treponema pertenue* of yaws and *T. carateum* of pinta as valid species that syphilis, yaws, pinta, bejel and other so-called "syphiloids" are all caused by *T. pallidum* and that the maladies named should be regarded as different patterns or syndromes of a disease that is fundamentally the same. Hudson recognizes that the differences between yaws and syphilis are often but not always so pronounced that a layman can distinguish them readily and he favors retention of the accepted names for the various clinical entities or syndromes caused by treponemes.

The reviewer accepts the conclusions and believes that physicians who are interested in any form of treponematoses will wish to read Hudson's presentation of the subject.

*The Ego and the Mechanisms of Defense*. By Anna Freud. Translated from the German by Cecil Baines. 12° cloth. 196 pp. New York: International Universities Press, Incorporated, 1946. \$4.00.

It must be stated at the outset that this small book will not be understood by the uninitiate or neophyte in psychiatry, particularly by those without a goodly quantity of psychoanalytic exposure. The text starts with what has been controversial in previous considerations of the functions and constituents of the ego. Then chapter by chapter attempts are made to depict the ego in the light of its defenses against many awe-inspiring opponents. This process of construction is carried on—as in many psychoanalytic presentations—as though the ego id and superego were as tangible and discrete "psychic institutions" as they seem to the analysts. The various well known ego defenses from instinctual "invasions" and superego attrition are described but with relatively little illustrative case material.

In many sections of the text the discussions point out so many controversial issues that the reader receives an impression of being in the midst of an informal psychoanalytic society subcommittee meeting whose chairman is proposing or dispensing with classifications. An example is the following quotation (Chapter IV):

According to the English School of analysis introjection and projection which in view should be assigned to the period after the ego has been differentiated from the outside world are the very processes by which the structure of the ego is developed and but for which differentiation would never have taken place—the chronology of psychic processes is still one of the most obscure fields of analytic theory. It will probably be best to abandon the attempt so to classify them and, instead, to study in detail the situations which call forth the defensive reactions.

To the reviewer, there did not appear to be any clear differentiation between anxiety and affect against which the ego must defend itself. Nor were the superego and the parental prohibitions against which the child may not transgress differentiated—childhood neurosis thus being arbitrarily separated from adult neurosis. In other sections the discussion did not distinguish between childhood and adult affect and anxiety.

Quite properly, the author stated (perhaps not emphatically enough) that the revelation of ego defenses makes the latter inoperative and may weaken the ego so as to advance a pathologic process.

The tried and tested case of Little Hans was again used to illustrate aggressive drives resulting fears and generalized fantasies—this time as ego defenses. Interesting deductive analyses of animal and circus fantasies and childhood stories are given as phases of the infantile(?) ego. These were



related to productive symptoms in the adult psychotic patient. It was also pointed out that parents frequently encourage escapes from reality in their children by inducing fantasies and adult impersonations of pleasurable type, the criteria of acceptance for these are then proportional to the consciousness of the symbols employed.

Interesting examples of reversal of aggression anxiety were given to illustrate identifications with the aggressor as developmental in superego formation.

The phenomena at puberty were related to those occurring in infantile and involuntal eras in a brief space (Chapter XI). Here the ego was again described as being rendered *hors de combat* between the immutable id and the inevitable superego, the result being the liberation of genital territory or its control by both ego and superego.

A brief discrete attempt was finally made to differentiate normal from pathologic features of ego defenses during puberty. The answer was qualified with provisos. The concluding chapter extols the ego by the magnitude of its defenses.

By an unusual amount of scrutiny the reviewer found many novel and useful items in this book. This may be possible for others quite well versed in analytic terminology. For those not so prepared the efforts necessary to learn from this text may outweigh its usefulness.

*Gastroenterology in General Practice*. By Louis Pelner, M.D. With the collaboration of Louis A. Held, M.D., and contributions from Alexander Lewitan, M.D., Samuel Waldman, M.D., and Siegfried W. Westing. 8°, cloth, 285 pp., with 108 illustrations and 15 tables. Springfield, Illinois: Charles C. Thomas, 1946. \$7.50.

This book is designed for the busy practitioner and medical student. It will not appeal to the expert in gastroenterology. It is planned as an everyday handbook rather than a complete reference work and contains much useful information, well classified and clearly presented, with rarely an opinion that can be questioned. It attempts to cover the whole subject of gastroenterology in about two hundred and sixty pages, including pathology, symptoms, physical examination, laboratory tests in detail and treatment, with the result that it presents rather brief pictures of some important subjects, such as the surgical treatment of bleeding ulcer and pyloric obstruction and the medical treatment of gastritis. Only two diseases of the liver are described in detail—portal cirrhosis and cholecystitis. Less frequent conditions, such as tumors of the liver and polyps and diverticula of the stomach and duodenum, are omitted, the importance of prepyloric ulcer in the stomach is not mentioned.

Tables of differential diagnosis and diets are freely used, and the book is fully illustrated with roentgenograms that, for the most part, are excellent. About two thirds of the book consists of text, and about a third of illustrations, tables and diet lists. It is possible that the use of tables is somewhat overdone.

The arrangement of chapters is unusual. The work begins with history taking, and one proceeds two thirds through the book before simple laboratory methods are reached. It would seem simpler to put all the diseases of the bowel together, and diseases of the liver and gall bladder in sequence. The author does well to limit the liver-function tests to thirteen or fourteen instead of the twenty to fifty that are sometimes mentioned. It is unfortunate that he has not included two of the simplest and best and most modern tests—the thymol turbidity test of the blood serum and the Harrison spot test for bilirubin in the urine.

Functional diseases of the gastrointestinal tract are mentioned throughout the volume. At the end of the book there are three chapters—one on psychosomatic symptoms of disease and the other on simple methods at the general practitioner can use. The preface and index are excellent.

*of the Bronchial Tree With special reference to lung abscess*. By R. C. Brock, M.S. (Lond.), M.D. 8°, cloth, 96 pp., with 142 illustrations. Ford University Press, 1946. \$12.00.

of this book successfully justifies his criticism. The physician has not yet learned to approach

the diseases of the lungs from the point of view of the segmental distribution of the bronchi. Only such knowledge will, he contends, enable a surgeon adequately to deal with conditions such as septic pneumonia and lung abscess. This is a stimulatingly instructive book. The exceptionally clear photographs—in color and in black and white—of metallic casts of the bronchial tree, made with the lungs in situ, the accurate drawings, and the clear bronchograms, both normal and abnormal, give considerable support to this point of view. This book deals with bronchial embolism and posture in relation to lung abscess, the level of the interlobar fissures of the lungs, the right upper lobe, the left upper lobe, the middle lobe, the lower lobes and the whole lung (anomalies and compound abscesses). The reviewer finds this book useful and provocative. The author's scholarly approach in presenting the material should place all physicians and surgeons in his debt. There can be no question that this book should be on the shelves of every medical-school and hospital library and in the personal libraries of those concerned with diseases of the chest.

*An Integrated Practice of Medicine*. By Harold T. Hyman, M.D. Four volumes and index volume. 8°, cloth, 4141 pp., with 1184 illustrations (305 in color) and 319 diagnostic tables. Philadelphia: W. B. Saunders Company, 1946. \$50.00.

This is an unusual system of medicine. Compiled largely by one writer, it comprises four large volumes and contains many millions of words. The task of putting it together must have been prodigious.

The author wished to supply the general practitioner with a modern handbook that would deal with all phases of modern medical work. No barriers of specialty practice have been permitted to obstruct the landscape. A pregnant mother or a patient with appendicitis, tuberculosis or any other ailment needs competent medical advice, and how to give this is described.

Clearly, it is impossible for any reviewer to do more than nibble at the various chapters in a work of such magnitude. This particular reviewer has enjoyed his acquaintance with the book as obtained in this manner. He believes that the thousands of physicians for whom it was written will like it, will learn much from it and will be grateful to the author.

*Your Rheumatism and Backaches*. By Joseph D. Wassersug, M.D. 8°, cloth, 254 pp. New York: Wilfred Funk, Incorporated, 1947. \$2.50.

This book is written to give the layman insight into the causes and treatments of symptoms and signs that are commonly labeled rheumatism or backache. It is a worthwhile endeavor for the occasional intelligent patient who requests further information to understand and follow treatment more effectively.

It is far more difficult to write a helpful and readable book for the laity than to write one for physicians. Most books of this type are written by men of wide clinical experience and deep understanding of the patient's problem. Because the author is a young man, a number of minor faults must be overlooked in this book. In later editions, less quoting from the writings of other men and a more critical analysis of the effectiveness of the treatments described, with illustrations drawn from the author's own experience, may be expected. An important omission—the most important in pre-health education—is the absence of any discussion of preventive measures that the patient may apply. Many insurance companies as well as a number of physicians have attempted discussions of the public-health aspects of these conditions.

The material comprising this book is well arranged. It is written in an interesting, readable style. It should be a helpful book for the lay reader.

*Parenteral Alimentations in Surgery With special reference to proteins and amino acids*. By Robert Elman, M.D. 8°, cloth, 284 pp., with 31 figures and 21 tables. New York: Paul B. Hoeber, Incorporated, 1946. \$4.50.

The frontiers of surgery were long restrained by a lack of appreciation of the significance of water, electrolyte and protein requirements in patients subjected to operation. During the past half century a body of knowledge regarding

basic needs and their fulfillment has accumulated. The clinical application of this information has contributed materially to the dramatic expanse of surgical endeavor and to a significant reduction in mortality and morbidity of major surgical procedures.

This text is a comprehensive discussion of the evolution of his phase of therapeutics by an authority whose original contributions to the development of parenteral protein formulation have been outstanding. It deals adequately with the biochemical basis of nutritional requirements as well as with the technical methods of their accomplishment by parenteral means.

**Cardiovascular Diseases** By David Scherf, M.D. and Linn Boyd, M.D. Second edition. 4°, cloth 478 pp. with 6 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$10.00.

This deservedly popular text has been improved by the inclusion of important new material. In particular a reasonably adequate treatment of the subject of rheumatic fever eliminates a serious omission in previous editions. The authors continue to pivot their discussion of diseases of the heart around specific structural abnormalities rather than etiologic factors. For instance, tricuspid stenosis, tricuspid regurgitation, mitral stenosis and mitral regurgitation are taken up as individual entities without emphasis on their common rheumatic origin. Although space is given to consideration of rare types of myocarditis, one looks in vain for mention of the important role that the myocardial lesion plays in the cardiac failure of chronic rheumatic valvular disease.

The book gives the impression of having been compiled from a series of lectures—each complete and excellent in itself but the whole lacking somewhat in integration. A good bibliography is appended to each chapter.

**Allergy in Theory and Practice** By Robert A. Cooke, M.D. In association with Horace S. Baldwin and others. 1°, cloth, 572 pp., with 1 color plate. Philadelphia: W. B. Saunders Company, 1946. \$8.00.

Each year the American College of Physicians sponsors a variety of postgraduate courses and one of the most popular is always been that on allergy directed by Dr. Robert A. Cooke, of New York City. This volume is a written account of the teaching to which his pupils have been thus exposed.

The book is excellent—a collaborative enterprise that ties together a vast amount of allergic information. Dr. Cooke, its leader, has written several chapters, including one on medical education and allergy that gives his ideas on so broad a problem with both clarity and brevity. The ordinary aspects of allergy are discussed by others of the team who are experts not only as clinicians but also as investigators and teachers.

Although most of the subjects that come under discussion are clinical in nature, the basic sciences on which allergy is founded are not forgotten. Hence the topics of chemistry, pathology and immunology receive due consideration. At the end of almost every chapter is a concise bibliography so that any student who wishes to dig more deeply into any phase of allergy receives good directions.

On the whole, this textbook is certain to be successful. All students, whether they are undergraduates or postgraduates, practitioners or specialists, will wish to study it. It is recommended wholeheartedly.

**Uterine Contractility in Pregnancy. A study of the contractions of pregnancy and labor under normal and experimental conditions.** By Douglas P. Murphy, M.D. 4°, cloth 134 pp., with 64 illustrations. Philadelphia: J. B. Lippincott Company, 1946. \$5.00.

The Larnard tocograph is an instrument that, when strapped to the abdomen of a pregnant woman, records by means of a pen writing on a moving strip of paper the frequency and amplitude of uterine contractions, as well as the degree of uterine tone. With this device Murphy has made three thousand one hundred and fifty-four observations on 1153 subjects and has arrived at the following conclusions: the character of uterine contractions varies in different persons;

the characteristic contractions of a given patient follow a distinctive pattern throughout pregnancy and labor; the first significant rise in uterine activity may be detected in the average woman at about the twenty-first week of pregnancy; and there is a period of relative quiescence up to the thirty-fourth week, one of nonrhythmic activity from the thirty-fifth to the thirty-eighth week and a final period of rhythmic activity in the last two weeks.

Murphy believes that if a subject exhibits uterine motility in early pregnancy or a high degree of rhythmicity during pregnancy she will manifest a satisfactory quality of uterine motility during labor. Inertia according to the author more frequently follows a poor pattern of contraction than an unsatisfactory quality of activity.

In the treatment of inertia Murphy states that pituitary extract may be used safely in the absence of fetopelvic disproportion if there is no excessive elevation of uterine tone as revealed by the tocograph.

Murphy's work with the tocograph is a distinct contribution toward the study of the physiology of pregnancy and labor. Its value, however, would have been enhanced if he had made more consecutive observations during both pregnancy and labor on a large number of patients. Moreover from the practical point of view much of the information furnished by the instrument can be obtained by the trained hand of the experienced obstetrician.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

**Nutritional and Vitamin Therapy in General Practice** By Edgar S. Gordon, M.D. Ph.D., associate professor of medicine, University of Wisconsin Medical School. Third edition. 8°, cloth 410 pp. with 47 figures and 23 tables. Chicago: Year Book Publishers, Incorporated, 1947. \$5.00.

The author published the first edition of this book in 1940 jointly with E. R. Sevringhaus and this third edition has been revised to include the new information in the literature since 1942. The volume includes material on dental problems in nutrition and on the economic side of clinical nutrition, as well as valuable tables on market lists for meals of low and moderate cost and on the nutritive values of selected foods. An appendix lists commercial vitamin preparations. A good index completes the volume which is well printed with a good type on light soft paper that is pleasing to the eye. It is worthy of note that the standard of medical book publication is steadily increasing in the post war era.

**Milk and Food Sanitation Practice** By H. S. Adams, B.S., chief Bureau of Environmental Hygiene, Division of Public Health, Minneapolis, and lecturer, School of Public Health, University of Minnesota. 8°, cloth 301 pp. with 65 illustrations. New York: The Commonwealth Fund, 1947. \$3.25.

This textbook is written for students of public health and workers in health departments who have charge of the sanitary control of milk and food supplies. The place of education in the sanitation program is stressed. The text is divided into two main divisions: milk sanitation and food sanitation. Each division has a bibliography of selected references. A chapter is devoted to a short history of milk control, with a full discussion of the severe epidemic of septic sore throat traceable to the use of raw milk in Lee, Massachusetts, in 1928. The following chapters consider the milk control program, the essentials of sanitary milk production, the various aspects of pasteurization, laboratory procedures used to evaluate milk supply and the sanitary control of frozen desserts. The food division is in three parts: the food control problem, with a discussion of federal, state and local inspection essentials of food-establishment sanitation and the instruction and training of food handlers. Eleven appendices are devoted to important supplementary information, among which may be mentioned essential and special food field equipment, food poisoning and infectious diseases, courses for the instruction of food handlers, the use of DDT as an in-

secticide and a list of films relating to milk and food sanitation. The material is well organized, the text well written, and the volume well published in every way. The book is recommended for all medical, public-health and public libraries and should prove valuable to all persons interested in the subject.

*Penicillin Therapy, including Streptomycin, Tyrothricin and Other Antibiotic Therapy* By John A. Kolmer, M.D., Dr. P.H., Sc.D., LL.D., L.H.D. Second edition. 8°, cloth, 339 pp., with 27 illustrations and 37 tables. New York: D. Appleton-Century Company, 1947. \$6.00.

This new edition has been largely revised and in part rewritten, and it has been enlarged by the addition of new material. New chapters have been added on the antibiotic agents other than penicillin and on antibiotic therapy in relation to veterinary medicine. In the first edition the clinical use of antibiotic agents in the treatment of various diseases was discussed from the standpoint of etiology, but in this edition the subject is discussed under pathologic entities. It is hoped that this arrangement will prove more valuable to clinicians. A long list of selected references is appended to each chapter. The volume is well printed with a good type on good paper and is recommended as a reference source for medical libraries and physicians.

*Parergon*. Third edition. Fo. paper, 208 pp. Evansville, Indiana: Mead Johnson and Company, 1947. \$5.00.

This edition reproduces the art of American physicians in various mediums. Two hundred and five pages are devoted to reproductions of the work. The quality is high, and some of the work is of a professional standard. There is a feature article on physicians as artists. The front cover is devoted to panels depicting Apollo, Aesculapius and Hygieia, and the back cover illustrates the restoration of the temple of Aesculapius at Epidauros. A number of Boston and Massachusetts physicians are represented in the selections. An index of artists is included in the volume. This book should be owned by every physician interested in the fine arts and should be in the historical collections of all medical libraries.

*The Pharmacopoeia of the United States of America*. By authority of the United States Pharmacopoeial Convention, Washington, 1940. Thirteenth revision (USP XIII). 8°, cloth, 957 pp. Easton, Pa.: Mack Publishing Company, 1947. \$8.00.

This revision is official from April 1, 1947. In the compilation of this edition the contents have been restricted to substances that reflect the best state of the medical knowledge of today and to preparations that may be most efficiently administered or used. For the first time English titles are given first, followed by the Latin equivalents. The revision of the *Pharmacopoeia* is continuous, and from time to time supplements listing new admissions are published. The excellence of publication has been maintained despite current difficulties. This standard reference work should be in all medical libraries.

*Studies from the Rockefeller Institute for Medical Research*. Reprints. Vol. 130. 8°, paper, 666 pp. New York: The Institute, 1947. \$2.00.

This volume is made up of reprints of articles originally published in various periodicals during the last part of 1946 and brought together in one volume for convenient reference. The articles have been repaged consecutively, and an author and a subject index supplied.

*Physician's Handbook*. By John Warkentin, Ph.D., M.D., and Jack D. Lange, M.S., M.D. Fourth edition. 12°, paper, 282 pp. Chicago: University Medical Publishers, 1946. \$1.50.

This pocket manual, first published in 1941, has been revised to include new material that has appeared since the publication of the last edition in 1944. The scope of the book has been extended to serve as a ready reference source for many types of medical and dental practice, and to include a relatively complete laboratory manual. Its popularity and usefulness are attested by the need of four editions in six years.

*Tuberculosis As it comes and goes*. By Edward W. Haye, M.D., associate professor of tuberculosis, College of Medicine, Evangelists, Los Angeles, member of the attending staff, Los Angeles County Hospital, Division of Tuberculosis, director of tuberculosis, Imperial County, California, an medical director and physician-in-charge, Maryknoll Sisters Sanatorium, Keane Sanatorium and Lair Sanatorium, Morrovia, California. With chapters by Laurence de Rycke, Ph.D. Second edition. 8°, cloth, 220 pp., with 92 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$3.75.

This popular manual designed for the sufferer from pulmonary tuberculosis is written in plain, nontechnical language and discusses the cause and nature of the disease and its treatment. The material is well organized and the chapters on classification and mechanical therapy are well illustrated with sketches from x-ray films. The short chapter on history could have been omitted without detracting from the value of the manual. The short quotation "Tuberculosis as old as mankind" would be sufficient for a book of this type and would carry more weight than the sketchy history. De Rycke has written two important chapters on suggestions to patients and to visitors. The text is printed with a beautiful, clear, large type on good paper, a delight to weary eye. The book should prove useful to patients as well as to physicians interested in pulmonary tuberculosis. It is recommended for public and medical libraries.

*Aging Successfully*. By George Lawton, M.D. 8°, cloth, 266 pp. New York: Columbia University Press, 1946. \$2.75.

This is a book for the layman and is not intended for the student or practitioner of geriatrics. It is written in a easy narrative style and covers the problems of advancing age in its many aspects. Dr. Lawton believes that the best time to prepare for old age is in childhood but that it is never too late to begin, although the task becomes increasingly difficult with the advancing years. To grow old successfully requires individual thought and effort. There is nothing that can completely erase illness, infirmity, poverty, loneliness, frustration and disaster. Of particular interest are the chapters on jobs after fifty, retirement, love at maturity, relations with younger persons and the philosophy of the aged. The author stresses the need of returning to an occupation or vocation. He discusses frankly and soundly the relations of old and young persons. Interspersed throughout the text are many stories pertinent to the problems under discussion. The reviewer, being technically near old age, is favorably impressed by the soundness of the advice and suggestions given by Dr. Lawton and by his analysis of the problems confronting the aging person in various situations. This book should be in all libraries, both general and medical, and can be read with profit by young and old of both sexes.

## NOTICES

### VAN METER PRIZE AWARD

The American Association for the Study of Goiter again offers the Van Meter Prize Award of three hundred dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. Provided essays of sufficient merit are presented in competition, the award will be made at the annual meeting of the association, which will be held in Toronto, Canada, May 6, 7 and 8, 1948.

The competing essays may cover either clinical or research investigations, should not exceed three thousand words in length and must be presented in English, a typewritten double-spaced copy should be sent to the corresponding secretary, Dr. T. C. Davison, 207 Doctors' Building, Atlanta 3, Georgia, not later than February 1, 1948.

A place will be reserved on the program of the annual meeting for presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual *Proceedings* of the association. This will not prevent its further publication, however, in any journal selected by the author.

(Notices continued on page xv)

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## STREPTOMYCIN THERAPY FOR CERTAIN INFECTIONS OF INTESTINAL ORIGIN\*

MAJOR EDWIN J. PULASKI, M.C., A.U.S., AND COLONEL WILLIAM H. AMSPACHER, M.C., A.U.S.

SEVERAL reports have already been published concerning the laboratory and clinical investigations on the efficacy of streptomycin in various infections carried out in Army hospitals under the auspices of the Surgeon General during the past eighteen months.<sup>1-3</sup> The purpose of the present communication is to enlarge on and bring up to date experience with treated infections of intestinal origin. The Army series is compared with the cumulative experience in these infections as recently reported by the Committee on Therapeutics and Other Agents of the National Research Council.<sup>4</sup>

### BRUCELLOSIS

The most recent report of the Committee revealed that, as of September, 1946, a total of 45 patients with brucellosis had been treated with streptomycin, of whom 15 showed no alteration in the course of the illness.<sup>5</sup> The other 30 patients showed a decrease in fever while under treatment. Two relapses occurred in the 29 patients in this group who were followed up from three to eight weeks. Five of the 30 apparently improved patients received less than 3 gm. of streptomycin daily, and 25 received 3 or 4 gm. daily for periods varying from five to sixteen days. Of the 15 unimproved patients, 5 received from 3 to 4 gm. daily, and the others received 2 gm. daily.

All cases investigated by the National Research Council were acute and culturally proved. Insufficient time has elapsed to permit a determination of the effect of streptomycin on the relapse rate in brucellosis, but its effect in the acute disease is evidently not pronounced. It was the opinion of the Committee that if streptomycin is used in brucellosis, the minimum dose should be at least 4 gm. daily for fourteen to twenty-one days.

Up to the present time 25 cases of brucellosis have been studied in the Army streptomycin program, of which 12 were acute and 13 chronic. The disease was classified as chronic when fever and symptoms had continued for a year or more. Blood cultures were positive for *Brucella* in 11 of the 12

acute cases, and the organisms were found to be sensitive to 0.5 to 1.0 microgm. per cubic centimeter of streptomycin. A bacteremia was present in 2 of the chronic cases. Most of the patients had positive skin reactions to killed *Brucella* organisms, and *Brucella* agglutinins in titers higher than 1:80 were obtained in the blood in all cases. Titers ranged from 1:320 to 1:5120 in the acute cases and from 1:80 to 1:1280 in the chronic cases.

Because these patients were observed over a period of fourteen months there was considerable variation in the amount of streptomycin that they received, as well as in the duration of treatment. By present standards some received too small doses for too short a time for beneficial results to be anticipated. The largest daily dose was 6 gm.,—in 2 cases, for a fourteen-day period,—but some patients received only 1 or 2 gm. daily for ten days. The intermittent intramuscular route was used in all cases.

The over-all results, regardless of whether large or small doses were used, indicated clearly that streptomycin is not effective in brucellosis. In the acute type of disease bacteremia disappeared in some, although not in all, cases while the drug was being administered, but recurrences were frequent, occurring in 5 cases. The relief of symptoms and improvement in appetite that some patients experienced under treatment could quite as well have been due to expected natural remissions and to psychologic factors as to streptomycin.

The following cases demonstrate typical responses to streptomycin therapy in brucellosis.

**CASE 1.** A 28-year-old Army officer had been in good health until December 12, 1945, when, during a leave, he developed chills, fever, night sweats, headaches, asthenia and anorexia. After ineffective treatment with sulfadiazine he was admitted to an Army regional hospital on January 4, 1946. When questioned he stated that he was not aware of having ingested raw milk or dairy products made from raw milk.

Physical examination showed a wan and listless man. The only other positive findings were a reddened pharynx and a palpable but not tender spleen.

Examination of the blood revealed a white-cell count of 6000, with 61 per cent lymphocytes. A blood culture grew colonies of *Brucella*.

Between January 4 and 15 asthenia and anorexia persisted and there were daily afternoon temperature elevations to 101° and 102°F. Sulfadiazine was begun on January 15.

\*From the Surgical Research Unit, Brooke General Hospital, Army Medical Center, Fort Sam Houston, Texas.

This project was carried out as a part of the study being made under the direction of the Army Medical Research and Development Board, Office of the Surgeon General.

and discontinued on January 27, after 68 gm had been administered. The temperature, which had fallen to normal, began to rise again on February 12, when a second course of sulfadiazine was begun, in combination with subcutaneous injections every 3rd day of a suspension of heat-killed *Brucella*. Blood cultures remained positive, and the patient showed no improvement. The combined therapy was discontinued on March 11, and 1 week later the patient was transferred to Halloran General Hospital.

Streptomycin therapy was begun on March 21 by the intramuscular route in doses of 0.5 gm every 4 hours. At the end of 21 days penicillin in doses of 40,000 units was added to each injection for an additional 5 days. Transfusions of citrated blood were also given. A mean blood serum level of 16 microgm per cubic centimeter was maintained, which, since the organism was sensitive in vitro to 0.5 microgm per cubic centimeter, meant that the blood level was many times the concentration required for bacteriostasis in vitro.

Throughout the period of treatment, there had been inconstant albumin and casts in the urine, and 24 days after treatment had been begun, the patient complained of dizziness and had difficulty in focusing his gaze. The streptomycin was discontinued 48 hours later. For the next 8 days the temperature rose only to 100°F daily, but on April 24 the elevations assumed the former level of 102 and 103°F. On April 29 the blood culture was again positive. The organisms recovered were inhibited by 0.5 microgm of streptomycin per cubic centimeter, just as they had been originally.

On May 21 streptomycin was resumed in the same intramuscular doses as had previously been given, and on the assumption that the drug had not previously reached all foci of infection, it was also given by mouth in daily doses of 2 gm. At the end of 1 week no obvious improvement had occurred under this regime. Streptomycin was then discontinued by mouth but was continued by the intramuscular route, and the patient was given, in addition, 6 gm of sulfadiazine daily. The temperature fell rapidly during the next 14 days, and as of December 1, there had been no recurrence. The patient felt well, had an excellent appetite and was gaining weight. No remission of similar length had occurred since the onset of illness, and it is believed that observation has been carried out for a sufficient length of time to regard the patient as apparently cured.

**CASE 2.** A 30-year-old bacteriologist was hospitalized on July 27, 1945, complaining of "high fever" and "weakness" for the preceding 48 hours. These symptoms had followed a mild episode of diarrhea. Temperature elevations persisted after hospitalization, and blood cultures on three different occasions were positive for *Brucella*, which was determined to be sensitive in vitro to 1 unit of streptomycin per cubic centimeter. Streptomycin therapy was begun on August 11, the patient receiving 0.2 gm intramuscularly every 4 hours for 10 days. The fever subsided by lysis, and the temperature reached normal on the 8th day of treatment. Three days later a thrombophlebitis developed in the deep veins of the left leg but gradually subsided. An episode of pneumonia, which began on September 8, responded promptly to penicillin.

During September two febrile episodes were associated with malaise and generalized lymphadenopathy, and a third episode of the same kind occurred in October. At that time a blood culture was again positive for *Brucella*. Streptomycin therapy was resumed, the patient receiving 0.33 gm by the intramuscular route every 4 hours for 10 days. The febrile course was completely unchanged, and there were daily temperature elevations to 102°F, but blood cultures became negative. The streptomycin level in the blood reached 16 units per cubic centimeter. Twenty-four hours after treatment had been discontinued the temperature returned to normal, but after a short interval it again became elevated. Since streptomycin was obviously of no value, it was not resumed. The patient has continued to run a course typical of undulant fever.

The course in Case 2 is characteristic of the uniform lack of response to streptomycin therapy in all acute and subacute cases of brucellosis. Case 1 is likewise typical of the response in acute cases: the blood cultures tended to remain positive regardless of the dose of streptomycin given and

the route of administration. These results are what might be expected. *Brucella* infections are characterized by the distribution of organisms through the lymphatic system and the blood stream, with localization in the gall bladder, spleen and lymph nodes, as well as in other structures. Previous studies on the disposition of streptomycin given parenterally, in cases in which death occurred in the course of treatment, indicate that the drug does not reach the lymph nodes in assayable amounts, whereas only small amounts can be recovered from the parenchyma of the spleen.<sup>2</sup> Levels in bile from the gall bladder and from the common duct are about a quarter as high as that in the blood serum. These observations are in accord with those of Reimann, Price and Elias<sup>7</sup> and Nichols.<sup>8</sup>

A remarkable feature of Case 1 is the fact that the susceptibility of the organisms to streptomycin, as shown by the blood culture, was in no way altered after twenty-six days of intensive therapy. Two possible explanations were postulated that the drug did not reach all foci of infection, and that the organisms were unique in not developing the expected drug-fastness usual under these circumstances. On the assumption that the first explanation was correct, streptomycin was given by mouth, in addition to its administration by the intramuscular route, but without effect on the course of the disease. On the assumption that the organisms were unique the culture was sent to the Merck Institute at Rahway, New Jersey, to determine whether fastness to streptomycin in vitro could be developed. The studies led to the conclusion that the organism isolated in this case followed the usual pattern and had become habituated to increasing concentrations of the drug. The findings therefore support the hypothesis that streptomycin does not reach the foci of infection in brucellosis in lethal concentrations.

In Case 1 the prompt response to the combined administration of streptomycin and sulfadiazine, after treatment by streptomycin alone had had no effect on the acute disease, led to the similar combined treatment of another patient, who had also shown no response to streptomycin alone. A similarly prompt and favorable response was obtained, and the patient has remained well over a six-month period of observation. It is still too early to state that permanent arrest of the disease was obtained in either case, but the combined method of treatment seems to deserve further trial as part of the general therapy of brucellosis. If it is employed, it is recommended that the dose of streptomycin be 0.5 gm intramuscularly and the dose of sulfadiazine 1 gm orally every four hours, and that treatment be continued for fourteen days or more.\*

\*Since the completion of this paper, 4 additional patients with the acute or bacteremic form of undulant fever have received combined streptomycin and sulfadiazine therapy for an average period of seventeen days. Three had a prompt remission, which has been sustained. In the fourth, a twenty-four-year-old woman, from whom *Brucella* could not be cultured, this therapy had no effect on the course of the disease.

## TYPHOID AND PARATYPHOID FEVERS

Schatz and his associates<sup>6</sup> were the first to report that streptomycin has a potent bacteriostatic action *in vitro* on the typhoid-dysentery-Salmonella group of pathogens, an observation that our studies subsequently confirmed.<sup>2</sup> A wide variation in range of sensitivity occurred when large numbers of the same species were examined. It is of considerable importance, however, that over 80 per cent of the organisms were found to be inhibited by 16 microgm per cubic centimeter, which indicates that the administration of 0.4 gm of streptomycin intra-

of streptomycin varying between 1 and 5 gm were given daily for five to nineteen days, the majority of patients received 4 gm daily for seven or eight days. Results were reported according to the time at which treatment was begun. In 18 of 28 cases in which treatment was begun before the eighteenth day of illness the temperature was normal before the twenty-eighth day, but in the other cases elevations persisted for periods ranging from twenty-nine to fifty-six days. In 25 cases in which treatment was begun after the eighteenth day temperature elevations persisted for twenty-eight days or more. In 1 case in which treatment was begun on the

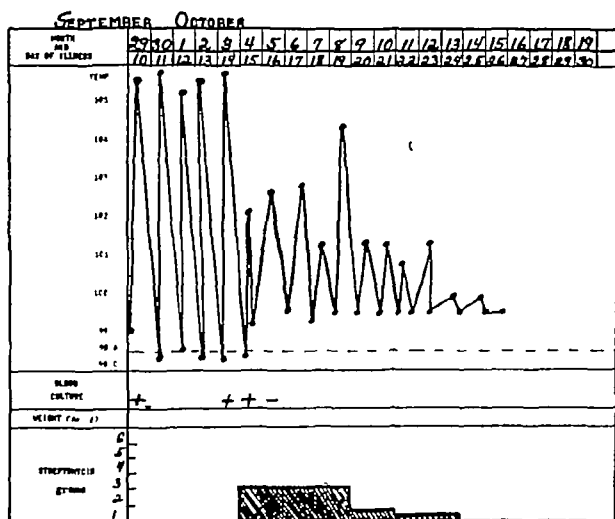


FIGURE 1

This patient, a twenty-eight-year-old woman, presented the classic signs and symptoms of typhoid fever, confirmed by positive blood and stool cultures. She derived no benefit from parenteral streptomycin therapy. The effectiveness of the drug administered orally is debatable since the organisms were reported resistant *in vitro*.

muscularly every four hours is sufficient to inhibit in blood serum the majority of the bacteria tested, since this dosage maintains the necessary blood level of the drug.

The fact that streptomycin is poorly absorbed from the gastrointestinal tract and is not inactivated by the contents of the bowel suggests that its oral use in certain susceptible infections is logical and useful. The oral administration of 4 gm daily by mouth causes 0.01 to 0.02 gm per gram of feces to appear in the stools and rapidly eliminates gram-negative bacteria from the bowel.<sup>7</sup>

The clinical experiences reported in the literature in typhoid and paratyphoid fevers are unfortunately somewhat at variance with results obtained in the laboratory.<sup>6-8</sup> In the 51 cases of typhoid fever studied by the National Research Council<sup>6</sup> doses

every eighth day of illness the temperature was normal by the twelfth day, the blood culture became negative during treatment, but the stools were still positive a month after therapy had been discontinued. In 15 cases the oral as well as the intramuscular route was used, without apparent difference in results.

The Committee reported that the number of patients treated was insufficient to determine whether the fatality rate in typhoid fever could be reduced by the use of streptomycin and believed that to date no evidence was at hand to indicate that streptomycin in doses of 4 gm daily could shorten the course of the disease. An interesting proof of this conclusion was supplied by the coincidence that the sister of a patient in the streptomycin-treated group developed typhoid fever simultane-

ously and that her course, without treatment, was identical with that of her sister, who had had treatment with streptomycin beginning on the fourteenth day and whose temperature had reached normal on the twenty-fourth day. The Committee pointed out the necessity of determining whether an earlier beginning of treatment (within the first seven days of illness) could shorten the duration of typhoid fever.

To date, results in 6 patients with acute typhoid fever, 3 typhoid carriers and 2 patients with paratyphoid infections in the Army streptomycin pro-

One patient died on the fourteenth day of therapy, presumably as the result of peritonitis from perforation of a Peyer's patch, which had occurred eleven days before the initiation of streptomycin therapy and which was followed by pneumonia. No autopsy was obtained.

Two of the typhoid carriers, both of whom were asymptomatic, received combined oral and systemic streptomycin therapy in doses of 4 and 2 gm respectively for a period of ten days. In both cases typhoid bacilli were still present in the feces after treatment. The remaining carrier had developed

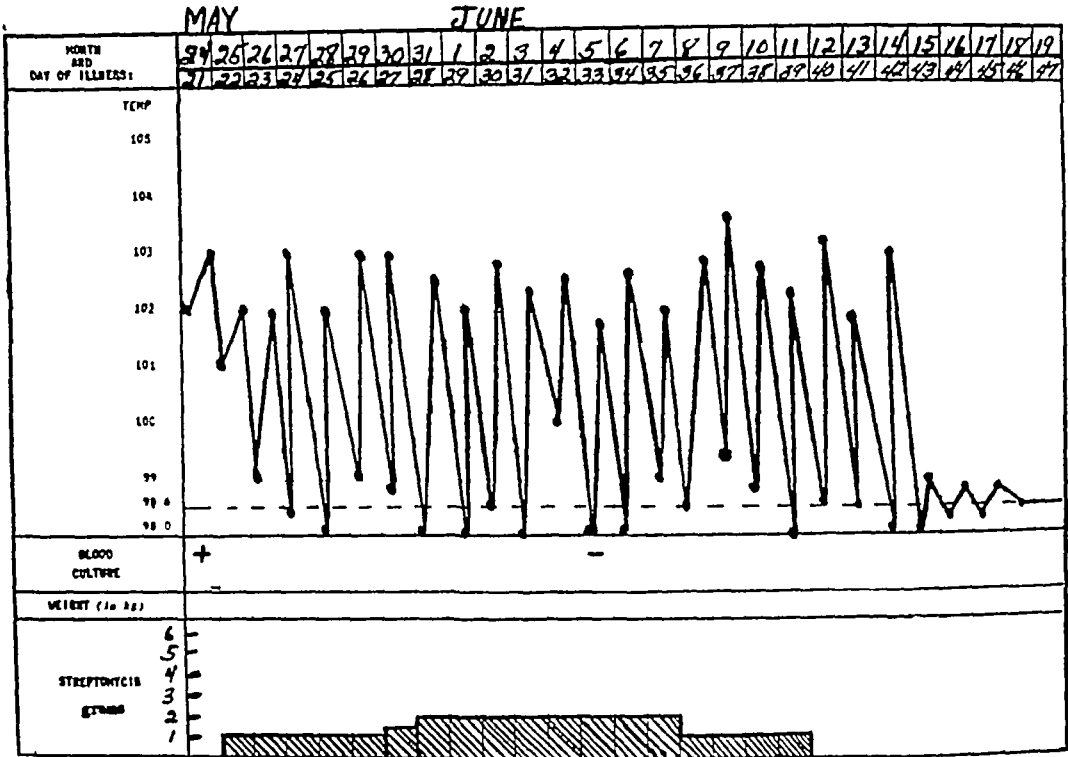


FIGURE 2

*This patient, a twenty-year-old woman, who had been immunized against typhoid fever three years before, developed severe typhoid septicemia with a toxic psychosis. Streptomycin therapy had no observable effect on the course of the illness.*

gram have been reviewed. The diagnosis in the acute cases was established by the culture of typhoid bacilli from the blood and the stools in every case and from the urine in 1.

Three of four strains of typhoid bacilli recovered in the acute infections were inhibited in vitro by 8 microgm of streptomycin per cubic centimeter, but the fourth strain proved drug-fast. All patients received from 2 to 4 gm of streptomycin daily for periods varying from eight to seventeen days. The combined oral and parenteral route was used in 3 cases, and the parenteral route alone in the other 3 cases. The accompanying charts (Fig 1-3) illustrate the diversity of the temperature response in relation to the dosage and schemes of dosage, as well as the effects of therapy on recovery of the etiologic agent from the blood and feces.

periostitis and osteitis of the right tibia four months after apparent recovery from typhoid fever. Typhoid bacilli were aspirated from the lesion and were also recovered from material obtained by biliary drainage. The diagnosis of typhoid osteitis was thus confirmed, and the carrier state established. Streptomycin was given for ten days in doses of 2.4 gm daily, after which the periostitis subsided and the symptoms disappeared. Four months later there was no clinical or roentgenologic evidence of infection of the bone, the Widal test became negative, and repeated cultures of urine, feces and bile showed no growth. In this case the disappearance of typhoid bacilli from the bile and from the lesion in the tibia was coincident with the administration of streptomycin.

In the following case streptomycin was apparently of value after sulfaguanidine had had no effect

**CASE 3** A 25-year-old soldier was hospitalized after an illness of 5 days characterized by headache, nausea, diarrhea abdominal pain and fever. *Salmonella paratyphi* was isolated from the stools but not from the blood. The administration of sulfaguanidine did not affect the course, and on the 10th day of the illness streptomycin was begun in oral doses of 0.5 gm. every 4 hours. Eighteen hours after the first dose the diarrhea and tenesmus abated, and the temperature fell to normal. A total of 4 gm. (eight doses) was given. The patient continued to make an uneventful recovery and has remained well over a 1 month period of observation.

The results of streptomycin therapy in the 6 cases of acute typhoid fever were disappointing. In only 1 case did the fever end within a sufficiently short time and recovery follow in such a manner as to suggest that the drug was responsible for the favorable outcome. It is perhaps significant that in this apparently successful case the patient, a five-year-old child, received the dosage usually given to an adult (Fig 3), which means that he received approximately three times as much streptomycin as any of the other patients were given. Both the oral and the parenteral routes were used. In the other 2 cases in which sensitivity to the organism was established streptomycin therapy was apparently without effect, and it is assumed that the active foci of infection were not reached. The efficacy of streptomycin in the remaining case is equivocal, since the treatment was begun when the disease was at the stage when recovery is ordinarily expected. As noted above, streptomycin by combined oral and systemic administration is theoretically the ideal treatment for enteric fever. The usual effects from systemic administration might be expected, and oral administration, because the drug is poorly absorbed from the gastrointestinal tract and is not inactivated in it, rapidly sterilizes the bowel of susceptible gram-negative bacilli. Published results of such combined treatment, however, are inconclusive and disappointing, as in our small series.

In 2 patients who were typhoid carriers streptomycin failed to eliminate typhoid bacilli from the feces. In a third carrier disappearance of typhoid bacilli from the bile and from a bone lesion coincided with the administration of streptomycin and may be attributed to its use. The administration of streptomycin was followed by a promptly favorable response and complete recovery in 1 patient with a paratyphoid infection.

#### ACUTE GASTROENTERITIS AND ENTEROCOLITIS

It is now quite well established that beneficial effects in varying degrees are obtained in bacillary dysentery by the use of sulfadiazine and sulfasuxidine but that these drugs are apparently of no value in *Salmonella* infections. Penicillin is not effective in the treatment of bacillary dysentery. The acute dysenteries respond promptly to chemo-

therapy. Chronic infections and the carrier state of *Shigella* dysentery require larger doses of the sulfonamides for longer periods before optimum results are secured. Failures of therapy, relapses and the development of the carrier state can be variously attributed to late institution of therapy, premature termination of therapy, insufficient dosage and the presence of drug-resistant bacteria.

The development of a new chemotherapeutic agent—especially one that is less toxic than the sulfonamides, can be used in smaller doses and is even more effective in the treatment of gastro-

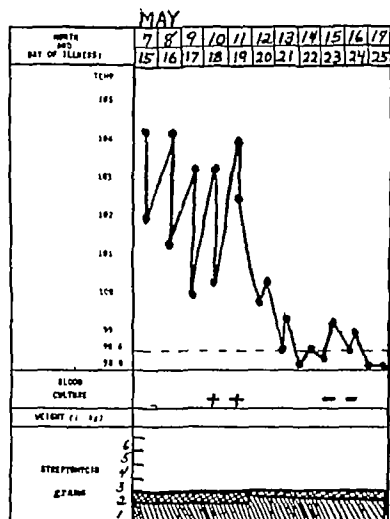


FIGURE 3

This five-year-old boy began to receive streptomycin therapy in large (adult) doses on the fifteenth day of his illness. Blood and stool cultures were negative within twenty-four hours after therapy was begun, and the temperature reached normal eight days later.

intestinal infections—naturally commands attention. Streptomycin seems to fulfill these criteria. Studies indicate that it is absorbed from the gastrointestinal tract in only small quantities, that it is excreted with the feces and that, as it is passed along to the rectum, it inhibits the growth of bacteria susceptible to it. The oral administration of 2 to 4 gm. daily alters the flora of the alimentary tract, especially the gram-negative bacteria, within forty-eight hours (Fig 4). To date we have not observed or seen reported in the literature toxic manifestations following the oral administration of streptomycin. Its use in disease of the gastrointestinal tract therefore seems indicated, especially as a substitute for the sulfonamides if in any case



they prove unsuitable by reason of ineffectiveness, toxicity, sensitivity of the patient or unavailability.

The most recent communication of the National Research Council<sup>6</sup> reported 2 cases of *Shigella* dysentery and 26 cases of *Salmonella* infection treated with streptomycin. Both patients with *Shigella* dysentery had previously been treated with sulfonamide drugs without result. Streptomycin, in a dosage of 15 gm daily by the intramuscular route for five days, was begun in the third month

became negative. The other 2 continued to have positive cultures and eventually died.

Seven of the 26 patients reported by the Council had enteric infections complicated by other conditions. Three had involvement of the lungs. Two of these had positive blood cultures when treatment was begun, 1 recovered, and 1 died. The third patient had negative blood cultures when treatment was begun and showed clinical improvement. Of 2 patients with *Salmonella* meningitis 1 recovered

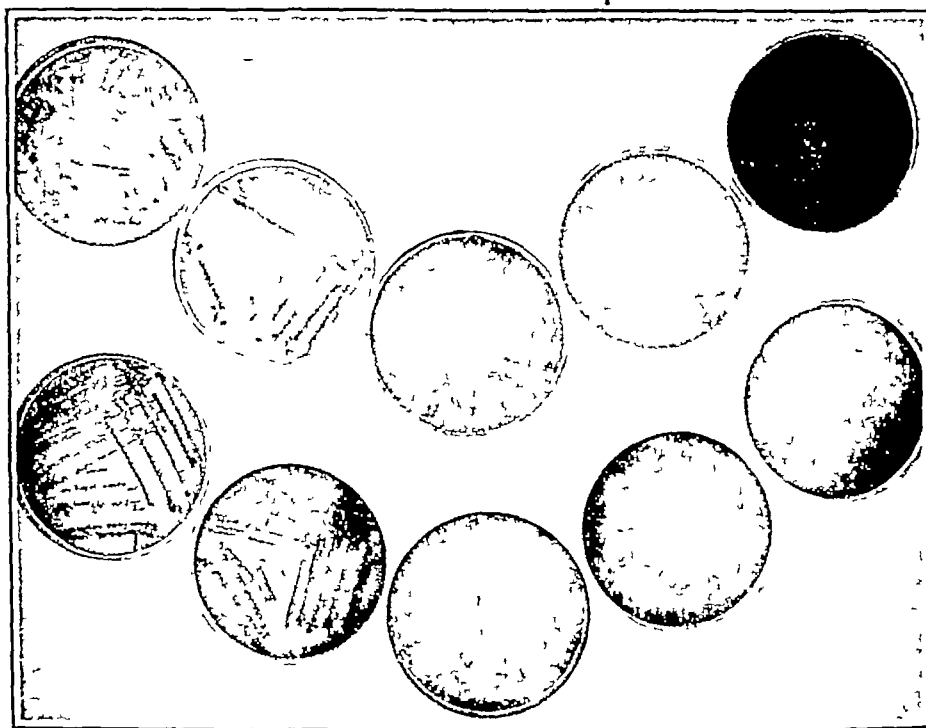


FIGURE 4 Effect of Oral Streptomycin on Fecal Flora

*These plate cultures of colostomy swabs were made at twenty-four-hour intervals, they show the effect of the ingestion of 0.5 gm of streptomycin every six hours. The drug effectively suppresses the fecal flora in forty-eight hours, but sterilization is not achieved, since it does not inhibit yeasts, fungi and certain gram-positive organisms, including Clostridia, which suggests that it might be desirable after forty-eight hours to combine oral penicillin therapy with streptomycin therapy. The last plates, made forty-eight hours after the drug had been discontinued, indicate that bacteriostasis was still present.*

of illness in 1 case and in the fifth month in the other. Stool cultures were positive in both cases before treatment and negative afterward. The period of follow-up observation was a month in 1 case and nine days in the other. Among the 26 patients with *Salmonella* infections 10 recovered under treatment, 2 improved under treatment and later recovered, 6 showed no improvement, and 8 died, 2 of whom had shown transient improvement in the course of treatment. Of the 19 patients with enteric involvement alone, 8 recovered, 7 were uninfluenced by treatment, and 5 died—1 of mesenteric thrombosis four weeks after treatment had been completed. Of the 5 patients in this group with bacteremia when streptomycin therapy was begun, 3 recovered and the blood cultures

under treatment, and 1, after transient improvement, died of hydrocephalus secondary to the infection. One patient was comatose when treatment was begun and died three days later, autopsy showed a complicating encephalitis. In a case in which the *Salmonella* infection was superimposed on ulcerative colitis three courses of streptomycin resulted in transient improvement, which was followed on each occasion by a recurrence of symptoms.

The average dose of streptomycin in these 26 cases was 3 gm for seven days. Treatment in 11 cases was started on the third to the sixth day of illness, and in the remainder from the seventh to the twenty-eighth day. When streptomycin therapy

was begun after the eighth day of illness only 1 patient recovered

The conclusion of the Council was that the high mortality in this series could be accounted for by the varying sensitivity to streptomycin of the various strains of *Salmonella* organisms, with the localization of the infection and complications of other diseases as possible additional factors. In view of the high mortality the recommendation was made that in *Salmonella* infections maximum doses of streptomycin be used as early as possible in the illness and that treatment be continued for at least fourteen days

### Bacillary Dysentery

Our experience with streptomycin therapy in bacillary dysentery includes 10 cases. The infecting organism was *Shigella paradysenteriae* (Sonne) in 4 cases and in 6 various subtypes of *Sh. paradysenteriae* (Flexner). Five patients were treated during the first attack of illness, and the remainder after previous episodes of diarrhea. In almost every case the patient had previously been treated with either absorbable sulfonamides, such as sulfadiazine and sulfathiazole, or the unabsorbable variety, such as sulfaguanidine and sulfasuxidine, or both. Streptomycin was given in doses of 1 to 4 gm daily for periods ranging from one to twelve days. The drug was administered orally in 2 cases, parenterally in 6 and in combination in 2.

In nearly every case the results were good to excellent. The causative bacilli disappeared from the feces, and symptomatic improvement was concomitant. The response was most dramatic in cases in which treatment was begun in the first attacks, and in patients with recurrent diarrheas who received combined oral and parenteral therapy amounting to 4 to 6 gm daily for twelve days or longer. No case of relapse has been recorded in periods of observation ranging from one to four months.

The following case is presented as typical of a successful result

**Case 4.** A 21-year-old medical corpsman on duty in the Pacific, had been well until November 13, 1944 when he began to suffer from abdominal cramps and diarrhea. Treatment with paregoric, bismuth and sulfaguanidine did not improve the symptoms. On admission to a station hospital on December 26 he was found to have hookworm ova (*Necator americanus*) in the stools but appropriate treatment produced no improvement in the original symptoms. On January 11, 1945, he was transferred to a general hospital, where he remained for 11 weeks. Treatment for hookworm was again carried out. The patient was relieved of cramps, although the diarrhea persisted, and was eventually returned to limited duty. On July 21 he was readmitted to the general hospital for recurrence of cramps and was returned to the United States where he was admitted to an Army general hospital on October 5. At that time he was having four or five loose stools daily. Stool cultures showed *Shigella paradysenteriae* (Flexner V and Z). Treatment with sulfaguanidine followed by sulfadiazine produced no results, and streptomycin therapy was begun on February 19, 1946, in doses of 0.25 gm every 4 hours and was continued for 10 days. On the 7th day of treatment the temperature rose to 101 and

on the 9th day to 103°F. On the 10th day a rash on the trunk was observed. The rash disappeared and the temperature fell to normal 24 hours after treatment had been completed. In the course of treatment the stool culture became negative, and the patient had formed stools for almost the first time since the beginning of the illness. He was well at the end of a 3 month period of observation. No definite cause for the temperature elevation or the rash that developed in the course of treatment could be found and both were attributed to a possible allergic reaction to streptomycin or to a possible impurity in the product.

### *Salmonella* Infections

Ten patients with enteric infections harboring *Salmonella* organisms in the stools received streptomycin therapy. Two had acute gastroenteritis and enterocolitis with blood cultures positive for *Salmonella* when treatment was begun. Combined oral and intramuscular streptomycin therapy for seven days resulted in elimination of the organisms from the blood stream and the feces, with relief of symptoms. No relapses were recorded. Three infants with severe diarrhea and *Salmonella* organisms in the stools were given streptomycin orally alone, in daily doses of 100 mg per kilogram of body weight for four to seven days, with attendant decrease in fluidity and number of stools and cultures negative for *Salmonella* for a follow-up period of three weeks. The remaining 5 patients had acute exacerbations of recurrent diarrhea, as well as stool cultures growing *Salmonella* organisms. Two patients were treated with streptomycin orally, without effect. Oral therapy was then combined with intramuscular streptomycin in 1 case, and three stool cultures became negative and remained so. Three patients with *Salmonella* organisms superimposed on a chronic enterocolitis received both oral and systemic streptomycin for a total dosage of 4 to 6 gm for ten to fourteen days. These patients obtained symptomatic relief during treatment, and cultures became and remained negative for *Salmonella*. Mild abdominal cramps and loose stools persisted, however, even though the *Salmonella* organisms did not reappear in follow-up cultures.

In the evaluation of these results of streptomycin therapy it must be borne in mind that acute bacillary dysentery and salmonellosis are frequently self-limiting diseases. On the other hand, the results in this small series of cases suggest that the therapeutic effect of this method is favorable. The observations reported are comparable to those made when the absorbable and nonabsorbable sulfonamides are used in susceptible cases. The results were usually favorable regardless of the method of administration employed.

Beneficial results were obtained in this series in acute infections caused by *Salmonella* and *Shigella* organisms that had proved resistant to sulfonamide therapy. Doses of 3 to 6 gm for periods ranging from three to sixteen days are probably adequate in most cases, but the larger amounts are recommended, for periods ranging from four to ten days,

to minimize the risk of development of streptomycin resistance. Since the offending bacteria are not confined to the lumen of the bowel but may penetrate into deep crevices and mesenteric lymph nodes, the combined oral and systemic method of administration seems more rational than the use of either route alone and is recommended. Evidence to date does not suggest that, as is advisable when the sulfonamides are used, streptomycin should be withheld until normal hydration is restored. Toxicity has not been observed following oral administration of the drug.

Streptomycin therapy was tested in 2 cases of amebic dysentery and proved of no value. The dosage was 5 gm daily for five and nine days, respectively, by the combined oral and systemic routes. The lack of results emphasizes the futility of employing streptomycin in any condition caused by organisms not susceptible to it.

### COLITIS

The most recent report of the National Research Council<sup>6</sup> includes only 1 case of ulcerative colitis on which a *Salmonella* infection was superimposed, as mentioned above. Three courses of streptomycin resulted in only transient improvement.

Our experience with streptomycin includes 16 cases of chronic idiopathic colitis and ileocolitis, in all of which the dysenteric disease had progressed from the acute to the chronic phase. In 1 case a culture revealed hemolytic streptococci. No causative organism could be isolated in any of the remaining cases. The diagnosis was based on the history, the symptomatology, positive roentgenologic observations, positive proctoscopic and sigmoidoscopic observations and the exclusion by proper tests of such specific conditions as bacillary dysentery, amebic colitis, tuberculous colitis, lymphopathia venereum and deficiency states.

Seven patients had chronic static disease. The 9 remaining patients were in the acute, active stage, with systemic manifestations. The lesions varied from a localized area in the most distal segment of the rectum to diffuse involvement of the entire large bowel. One patient had, in addition to colitis, a segmental ileitis for which an ileocolostomy had been performed. The 9 patients with extensive involvement were moderately to seriously ill.

All the patients had had a variety of previous treatments, including sulfonamide and penicillin with either no response or with only slight improvement. This is in agreement with our experience. Amelioration of symptoms has sometimes been obtained by the use of the sulfonamides and penicillin, but no significant series has been reported in which lasting remission could be directly attributed to chemotherapy. Streptomycin was given in doses ranging from as little as 1 gm up to 2 gm at intervals of three to six

hours, by the intramuscular or oral route or by both routes, for periods ranging from four to sixty-two days. Penicillin was also given in 1 case. Improvement was considered to have occurred if there was a reduction in the number of stools, a decrease in or disappearance of blood in the stools, and relief from the concomitant symptoms of toxemia. On this basis temporary improvement was observed in all acute cases except 1 in which a hemolytic streptococcus was implicated as the etiologic agent. In the cases of chronic static disease some improvement usually occurred during therapy, but it was generally undramatic and seldom permanent. The following case is not atypical.

**CASE 5** A 25-year-old officer developed diarrhea in October, 1945, with bright-red blood in the stools. He was hospitalized promptly but continued to have two to fifteen bowel movements daily, many of which contained blood. Cysts of *Endamoeba histolytica* were found in the stools on a number of occasions, and significant titers (1:320) for *Shigella paradyserteriae* (Flexner Y) antibodies were demonstrated in the blood. There was positive roentgenologic and sigmoidoscopic evidence of ulcerative colitis. Courses of antiamebic drugs, sulfathiazole and penicillin, alone and in combination, failed to influence the course of the disease. Repeated transfusions of blood and plasma were necessary for correction of a marked anemia.

Streptomycin therapy was begun on May 29, 1946, in doses of 0.5 gm orally every 3 hours and was continued for 5 days. The drug was discontinued after an increase in diarrhea accompanied by temperature elevations had developed. On June 28 a second course of streptomycin was begun in the same dosage and was continued for 14 days. The dosage employed effectively eliminated the susceptible fecal flora but had no effect on the temperature elevations and diarrhea. A third course was begun on July 29, the drug being given intramuscularly in dosages of 0.4 gm every 4 hours for 7 days. There was no alteration in the course of the disease or in the bacteriologic findings, and streptomycin therapy was permanently discontinued.

In evaluating the results of streptomycin in colitis it is necessary to bear in mind two points: whether the streptomycin therapy is a part of the medical regimen in a case in which surgery is not required, or whether it is employed in the hope of controlling the active phase of the disease, so that resection can be more safely undertaken, and just what is expected from treatment. Whatever the objective of therapy, it is obvious that no chemotherapeutic agent can be expected to restore to normal the physiologic function of an intestine that has undergone irreversible changes and has become contracted and deformed by disease of long standing. All that any drug can be expected to accomplish under such circumstances is to control symptoms due to active infection.

The majority of patients treated in this small series derived some benefit during treatment with streptomycin, but over-all findings are contradictory and no particular optimism seems warranted; it could scarcely have been expected. The impression is gained from a study of these cases that future evaluation of streptomycin therapy should be on the basis of longer courses of combined oral and systemic administration.

## EPIDEMIC DIARRHEA

The report of the National Research Council\* apparently includes no cases of epidemic diarrhea in infants. The present study comprises 13 cases of this type of diarrhea. Eight infants were received from an Army transport, which had been the scene of an outbreak of the disease, and 4 were serious cases of nonspecific gastroenteritis complicated by dehydration, toxemia and varying degrees of malnutrition that, in 2 cases, amounted to a state of marasmus. The thirteenth patient had also had gastroenteritis, and was 1 of 3 controls, she was treated with streptomycin when her condition failed to improve under the usual treatment. No *Shigella* or *Salmonella* organisms of the usual pathogenic variety could be recovered from any of these cases. *Proteus morganii* and *Pr. vulgaris* predominated in all cases, but since these organisms are present in normal stools and tend to overgrow other bacteria readily, it is difficult to incriminate them as the etiologic agents. It is believed with reasonable certainty that no single organism was responsible for the infection in any case in the group.

Because of a lack of previous experience with streptomycin in epidemic infantile diarrhea, the first 7 infants received from the Army transport were treated with small doses of the drug. Two died, forty-eight and seventy-two hours, respectively, after the beginning of therapy, as the result of severe toxemia and central-nervous-system involvement. The remaining patients were discharged in good condition and on full diets between the fifteenth and thirtieth days after admission, hospitalization was prolonged in some cases because of extensive weight loss. All these children received daily doses of streptomycin varying from 0.1 to 0.2 gm. per kilogram of body weight at four-hour intervals over periods varying from two to ten days. The eighth patient received from the Army transport was given 0.1-gm. doses at four-hour intervals for six days. Two of 3 patients with infantile diarrhea used as controls while these 8 children were under treatment with streptomycin did well under the usual treatment. The third, after a period of improvement under the usual routine, regressed and became critically ill, but recovered after the use of large doses of streptomycin.

Two babies with nonspecific gastroenteritis associated with malnutrition and dehydration, after failure of the usual treatment, were given streptomycin in daily doses of 0.3 to 0.6 gm. per kilogram of body weight and were placed on full diets at the same time. One made a prompt and dramatic recovery. The other continued to have diarrhea and fever until the daily dosage of streptomycin was raised from 0.3 to 0.6 gm. per kilogram of body weight. Although the diarrhea was controlled and the temperature began to fall, death eventually occurred from pneumonia and heart failure. Two

other infants with nonspecific gastroenteritis were treated early and vigorously with streptomycin in daily doses of 0.12 and 0.25 gm. per kilogram of body weight and showed prompt improvement. One child was discharged within twelve days, after a gain of 1 pound, 5 ounces, over a period of only eight days. When treatment was begun she was moribund, being in a state of respiratory and circulatory collapse, nervous-system involvement was manifested by convulsions, spasticity, facial paralysis, stupor and coma. When she was discharged the only residuum was a mild facial palsy.

One child, in another Army hospital, was treated by doses of 30 mg. of streptomycin orally every hour for one hundred hours. Diarrhea was controlled but recurred briefly after therapy had been discontinued. Larger doses given over a longer period might have been more promptly effective.

No conclusions regarding the value of streptomycin therapy in epidemic diarrhea can be drawn from so small a series of cases. On the other hand, it was the considered opinion of Major Irvin J. Cohen, under whom these cases were handled, that at least 4 of the 13 children are alive today because of streptomycin, which in all cases seemed to shorten the period of illness, control starvation and malnutrition and reduce the hospital stay. When a proper routine of usage has been established, a demonstrable reduction in mortality may reasonably be expected. Further studies should be conducted on infants with epidemic infantile diarrhea and nonspecific gastroenteritis by the following regimen: parenteral fluids, including blood and plasma to combat shock and restore water, electrolyte and protein balance, early oral feedings of 72 to 125 calories per kilogram of body weight if vomiting is absent, and streptomycin in adequate doses, 0.5 gm. per kilogram of body weight being regarded as the minimal daily dose. Dosages up to 1.0 gm. per kilogram of body weight should be utilized in critically ill children, regardless of age. The drug should be continued for at least a week after a satisfactory response has been obtained.

## SUMMARY

The present report enlarges on and brings up to date certain streptomycin-treated cases of intestinal origin observed in the Army streptomycin program. For comparative purposes brief statements are made concerning the report of the Committee on Therapeutics and other Agents of the National Research Council on the same types of infection.

Generally speaking, the results of streptomycin therapy in acute and chronic brucellosis were poor, although in 2 acute cases in which streptomycin therapy and sulfonamide therapy were combined apparent cures were achieved. The results in acute typhoid fever were disappointing, and in 2 of 3 typhoid carriers treatment was a failure. A patient with dysenteroid paratyphoid fever recovered

promptly. The results of treatment in enteritides due to *Salmonella* and *Shigella* organisms were generally favorable, but in nonspecific ulcerative colitis they were generally undramatic, or at least equivocal. Results in infantile diarrhea, although some deaths occurred, were usually good and sometimes dramatic.

Dosage, routes of administration and similar details are discussed, and lines of future investigation are suggested.

The conclusion continues to be warranted that in infections caused by organisms susceptible to streptomycin the results of treatment are likely to be good if the drug can be brought into contact with all foci of infection. If the organisms are not susceptible to streptomycin, treatment is without value.

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## GOLD THERAPY IN RHEUMATOID ARTHRITIS\*

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**T**REATMENT of rheumatoid arthritis with gold compounds, initiated in Europe twenty years ago, has gradually grown in favor in American medicine during the past ten years. Recently, Fraser<sup>1</sup> condensed the literature on chrysotherapy in this disease and noted that most observers report a favorable response in 70 to 80 per cent of patients. Short, Beckman and Bauer<sup>2</sup> found more than forty publications on gold therapy in the English literature up to 1946, almost all of which were favorable toward this type of treatment. Since these recent summaries are available, a review of the literature on this subject is not attempted in this report. When the publication of Short, Beckman and Bauer appeared, again raising the question of efficacy, we were engaged in reviewing six years' experience with gold treatment in the Arthritis Clinic, Indianapolis City Hospital. The results revealed in this survey seem sufficiently comparable to those reported by the Boston group to justify publication of the findings.

### TREATMENT

The chronic nature of rheumatoid arthritis and its tendency to spontaneous improvement or exacerbation make difficult the accurate evaluation of progress. This is further complicated by the optimistic nature of many patients who are prone to symptomatic improvement with any treatment.

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administered with a hopeful attitude on the part of the physician. Aware of its shortcomings but in the hope of providing a standard method of evaluation, we adopted a modification of the "yardstick" of Bayles and Hall.<sup>3</sup> To illustrate the method used, a portion of one patient's record is presented in Figure 1. As indicated in the key, four objective findings—mobility, activity of disease, static deformity and extent of involvement—are translated into a numerical value. Similarly, laboratory findings and subjective symptoms are assigned a number. The total of all six items provides an index number, with which the index obtained on subsequent examinations is compared. In the estimation of progress a change of two points in the index is considered to be significant. Hence, a value that decreases from 12 to 10 is accepted as indicative of improvement, and, conversely, a change from 12 to 14 is taken as evidence of progressing disease. The method appears to be helpful in the long-term and follow-up study necessary in the evaluation of therapy.

With the use of the index system the records of 52 patients treated with gold were examined. Five of these were eliminated at the outset because the patients had received less than 100 mg. of gold salts. The records in the remaining cases form the basis for this report. All patients had a definite diagnosis of active rheumatoid arthritis. All were adults ranging in age from twenty to sixty-four years at the time treatment was begun. There were 34 women and 13 men, representing a sex ratio of a little less than 3:1. The longest period of

observation was six years, but all patients were followed for more than eighteen months. The stage of disease at the time treatment was initiated varied from less than two years' duration in 18 cases, or 38 per cent, to the later stages of the disease in 29, or 62 per cent. Patients with more advanced involvement had been treated elsewhere

was followed, with most patients receiving 50 mg of gold sodium thiomalate or 25 mg of actual gold. The total amount per course has remained at 1000 mg of the salt, but in most patients now under treatment, maintenance therapy of 25 mg every two weeks has been continued indefinitely after a course has been completed. In addition,

NAME — L. M		HOSP No — 167923						BIRTH DATE — 1906	
DATE	BRIEF CLINICAL HISTORY Onset May, 1943 with painful swollen hot left knee Gradually progressed to involve proximal interphalanges, elbows and ankles No previous history of joint disease						GOLD (MG)	INDEX	
	M	A	D	E	L	S			
June, 1943	0	2	1	2	4	1	0	10	
January, 1944	3	2	2	2	4	3	0	17	
June, 1944	1	2	1	2	3	2	1310	11	
June, 1945	1	2	1	2	4	1	1120	11	
June, 1946	0	2	1	2	4	1	625	10	

FIGURE 1 Reproduction of a Patient's Chart

The key is as follows:

- M — Mobility: 0 — employable; 1 — ambulatory (able to get about alone); 2 — confined to one floor, bed and chair without assistance; 3 — confined to bed needing part-time assistance (able to feed self and so forth); 4 — confined to bed needing full time assistance (helpless).
- A — Activity of disease: 0 — no activity (history of having had disease); 1 — presence of disease but no objective signs of activity at present; 2 — intermittent heat, swelling and effusions in joints; 3 — appearance of subcutaneous nodules, persistent heat, swelling, tenderness and effusions in joints with mild to moderate muscle atrophy and slow joint destruction; 4 — fulminating rapid course of disease with joint destruction, fever, rapid weight loss and so forth.
- D — Deformity of static nature (made on worst joint): 0 — none; 1 — periarticular thickening, painless fluid or crepitus on motion; 2 — limitation of motion; 3 — subluxation; 4 — ankylosis or flail joint.
- E — Extent of joint involvement (percentage of joints involved): 0 — none; 1 — 0 to 24; 2 — 25 to 49; 3 — 50 to 74; 4 — 75 to 100.
- L — Laboratory evaluation: 0 — no abnormality; 1 — slight increase in sedimentation rate (Wintrobe method, +5 mm) or slight anemia, or both; 2 — moderate change in sedimentation rate (+10 mm); 3 — severe change in sedimentation rate (+20 mm); 4 — extreme change in sedimentation rate (+30 mm or more).
- S — Subjective symptoms: 0 — none; 1 — intermittent mild to moderate malaise, weakness, fatigue and joint pain; 2 — continuous and mild to moderate for the above symptoms; 3 — intermittent and severe or continuous and moderate for the above symptoms; 4 — continuous and severe for the above symptoms.

with the usual variety of remedies, but none had previously been treated with gold.

During the first years of chrysotherapy the customary weekly dose of 100 mg of gold salts was given to a total of 1000 mg per "course." Gold sodium thiomalate (Myochrysine) was the standard compound, although for about a year gold acetyl cystein was given. Since both compounds contain 50 per cent gold, they are considered comparable therapeutic agents. During the past four years, the current practice of giving lower weekly doses

acetyl salicylic acid has been used freely to control pain, and application of heat to affected joints has been a daily routine with the majority of patients.

## RESULTS

With classification on the basis of the total amount of gold salts administered, the results of treatment are summarized in Table 1. It is interesting that 8 patients who were given only 500 to 1000 mg showed the greatest percentage improvement of any group — in fact, 17 per cent greater

than that in the group of 10 patients who were given more than 3000 mg. The next greatest improvement was in the 9 patients who received less than 1500 mg. This suggests that the first course of gold is the most effective, a finding noted by others.<sup>4</sup> It is interesting that 6 of the improved patients, 5 of those in the unchanged group, and all 7 listed as failures had been victims of the disease for less than two years. With these 18 patients as a group representing the earlier stages of rheumatoid arthritis, 33 per cent were improved, 28 per cent were unchanged, and 38 per cent

The fifth patient, a forty-two-year-old woman, developed a mild dermatitis after receiving 400 mg of gold salts. This was not recognized as a toxic effect of gold, and treatment was continued. When 625 mg. had been given the patient rapidly developed exfoliative dermatitis. After five months' hospitalization for the skin condition, she died, the disease having been further complicated by epilepsy and latent syphilis. This fatal case must obviously be attributed to gold poisoning.

Evidences of gold toxicity were seen in 29 patients, or 62 per cent, of the entire group. Skin

TABLE 1 Results of Treatment

DOSAGE OF GOLD SALT*	NO OF PATIENTS	IMPROVEMENT		NO CHANGE		FAILURE†		RELAPSE AFTER IMPROVEMENT		DEATH		REACTION TO GOLD	
		NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE	NO OF CASES	PER-CENTAGE
mg													
Less than 500	7	0	0	7	100	0	0	0		2	29	5	71
500-999	8	4	50	4	50	0	0	1	12	1	12	7	88
1000-1499	9	3	33	6	66	0	0	1	11	2	22	6	66
1500-1999	7	1	14	3	43	3	43	0	0	0	0	3	43
2000-2999	6	1	17	4	67	1	17	0	0	0	0	3	50
3000 or more	10	2	20	5	50	3	30	0	0	0	0	5	50
Totals	47	11		29		7		2		5		29	
Averages			23		62		15		4		11		62

\*Salt containing 50 per cent gold  
†Patient worse after therapy

became worse with gold therapy. It is only fair to state that 62 per cent of the entire group showed no measurable change for better or for worse as a result of treatment. A possible effect of gold in preventing advance of the disease may thereby be implied.

Toxic Effects

During the six-year period 5 patients died, but only 1 fatal case seemed definitely attributable to gold toxicity. One man died at the age of sixty-seven years because of congestive heart failure three years after receiving a total of 400 mg of gold salts. A woman died at the age of forty-five years with a questionable diagnosis of amyloidosis. She had completed a course of 1150 mg of gold salts three years before death. Treatment had been discontinued because of an exfoliative dermatitis apparently due to gold, but she had recovered from this within six months after treatment had been stopped and two and a half years before death. A forty-two-year-old woman developed a mild dermatitis after having received 1215 mg of gold salts. She died three months later after surgery for acute bowel obstruction. Another woman, aged sixty-three years, had received only 95 mg of gold salts when she developed a mild purpura. Treatment was stopped, and she failed to return to the clinic. A follow-up letter six months later revealed that she had recently died, presumably of cerebral thrombosis.

reactions were observed quite frequently and were the reason for temporary or permanent withdrawal of the drug in 25 cases. In most cases only a mild pruritus or limited skin eruption was seen, and often after the skin had become normal treatment was cautiously resumed. Some of these patients were able to complete the course of therapy without further side-effects. Exfoliative dermatitis was seen in only 2 patients, and 2 others exhibited evidence of purpura. Treatment was discontinued temporarily in 2 cases because of neutropenia. Several patients showed evidence of renal irritation in the form of transitory proteinuria or microscopical hematuria. Diarrhea thought to be due to gold was occasionally observed.

DISCUSSION

In these patients treated with gold salts the results have not approached those reported in the majority of publications on this subject. An explanation may be found in the longer period during which the patients were observed. In many cases apparent improvement was seen after treatment, but in few cases was there a lasting effect. In this report no attempt has been made to discuss separately patients who improved only to relapse, for it is believed that a period of more or less temporary relief is of little consequence in this disease.

The percentage of improvement in this series happens to be the same as the 23 per cent net

improvement reported by Short, Beckman and Bauer<sup>2</sup> in 35 cases. In contrast, through the use of general and orthopedic treatment, these authors obtained improvement in 52.9 per cent of a larger series of 274 cases without the risk that is always associated with gold therapy.

### SUMMARY

Forty-seven patients with active rheumatoid arthritis were observed for periods of eighteen months to six years. All received gold therapy in amounts ranging from less than 500 to more than 3000 mg of a salt containing 50 per cent gold. Those who continued in an improved state after treatment constituted only 23 per cent of the total,

whereas 62 per cent showed no appreciable change, and 15 per cent became worse.

A high incidence of toxic reactions to gold was noted, 62 per cent of patients having been involved. Although most of these side-effects were of little consequence, there were 2 cases of exfoliative dermatitis, with 1 death.

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## TREATMENT OF ACUTE UREMIA BY PERITONEAL LAVAGE

### Report of a Case

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THE treatment of uremia has long been directed toward symptomatic relief, healing of the underlying renal lesion and in acute and presumably temporary cases, maintenance of life long enough to allow the kidneys to reassume their essential functions. It is toward the last objective that attempts have been made by numerous workers to supply a temporary "substitute" for the kidneys, which would maintain excretion of uremic metabolites, whose retention is fatal to the organism. In a review of the chemical changes known to occur in uremia, Harrison and Mason<sup>1</sup> stressed the importance of increased blood and tissue concentrations of urea, free phenols and guanidine-like substances, the depression of ionized-calcium concentrations through the accumulation of phosphate, citrate and oxalate, the debilitating effects of water and chloride deprivation, particularly on tissue proteins, the profound disturbances in acid-base balance due to loss of sodium ions and accumulation of organic and inorganic acids, and the hypothetical toxic effects of many other retained substances as yet incompletely identified. Since theoretically modifications in the equilibria of all the substances named above might be effected by indirect contact, through a semipermeable membrane, with a solution of different composition, repeated experiments have been made to bring the circulating blood of uremic organisms into such osmotic contact with a prepared solution.

The technic of removal of diffusible substances from the circulating blood by dialysis through a celloidin membrane surrounded by various solutions of crystalloids was successfully demonstrated in 1912 by Abel, Rowntree and Turner<sup>2</sup> and reported in detail in 1914. In the experiments performed, meas-

urable amounts of nonprotein nitrogenous substances were removed from the circulating blood of normal rabbits, and orally administered salicylates were recovered from the blood of dogs. In 1923 Ganter<sup>3</sup> reported the use of the peritoneum in human beings as a "natural" semipermeable membrane, a hypotonic solution being introduced into the abdominal cavity in an attempt to remove uremic substances from the blood. In a patient with chronic nephritis this attempt at maintaining life was unsuccessful. Thereafter, Rosenak and Siwon,<sup>4</sup> von Jenv,<sup>5</sup> Balazs and Rosenak,<sup>6</sup> Bliss, Kastler and Nadler,<sup>7</sup> Haam and Fine,<sup>8</sup> Seligman, Frank and Fine<sup>9</sup> and Abbott and Shea<sup>10</sup> demonstrated, in mammals rendered uremic by nephrectomy or ureteral ligation, that significant amounts of "uremic substances" could be removed from the circulating blood with temporary prolongation of life. The method generally used was intermittent injection into and withdrawal from the peritoneal cavity of various solutions approximating the crystalloid content and reaction of intercellular fluid. In a study of various solutions by Abbott and Shea<sup>10</sup> the most satisfactory fluid for use in dogs rendered uremic by bilateral nephrectomy was found to be Hartmann's solution with added sodium bicarbonate, monosodium phosphate, magnesium chloride and dextrose in concentrations up to 5 per cent.

Following Ganter's<sup>3</sup> effort to relieve uremia in a human patient by peritoneal dialysis, several attempts were made by Heusser and Werder,<sup>11</sup> Balazs and Rosenak,<sup>6</sup> Wear, Sisk and Trinkle,<sup>12</sup> Rhoads<sup>13</sup> and Fine, Frank and Seligman,<sup>9</sup> who used various modifications in solution and technic of perfusion of the peritoneal cavity. Of the 17 patients whose cases are known to have been reported prior to the



present communication, only 2 have survived peritoneal dialysis. One was a case of "reflex anuria," with bladder calculus reported by Wear et al<sup>12</sup> in which the nonprotein nitrogen was never above 71 mg per 100 cc, and the alkali reserve was 51 vol per cent. Since the bladder obstruction was relieved by catheterization and suprapubic cystotomy with subsequent profuse diuresis, the role of peritoneal dialysis was less clear cut in this case than in other reported cases. The other successful case reported by Frank, Seligman and Fine<sup>15</sup> was elsewhere compared with 3 cases treated by the same authors in which death followed the procedure.<sup>14</sup> This case was that of a fifty-one-year-old man with acute sulfathiazole anuria and uremia who recovered kidney function after seven days of continuous peritoneal irrigation with modified mammalian Tyrode's solution, in addition to the usual supportive measures.

The patient in the following case was treated through the courtesy of Drs Frank and Seligman, of the Beth Israel Hospital, Boston, who made available all necessary apparatus and technical data and offered invaluable advice in the conduct of therapy.

J A Y, a 37-year-old single military prisoner was admitted to an Army hospital on July 8, 1946, complaining of burning abdominal and chest pain and hemorrhage by mouth, rectum and urethra, of about 3 hours' duration. A history was subsequently obtained that the soldier had been absent without leave and drinking heavily, with a markedly inadequate diet, for about 1 month and that, because of an acute situational depression, he had taken seven tablets (3.5 gm) of mercuric chloride by mouth in a suicidal attempt. Within 30 minutes he had begun to vomit a bright, bluish-green liquid containing no undigested tablets, he was transferred to the hospital after routine emergency treatment with milk and egg white by mouth.

The family and past histories were noncontributory. Psychiatric examination throughout the hospital stay showed the patient to be emotionally unstable and immature, but not psychotic.

Physical examination revealed a well developed and well nourished man who appeared pale, prostrated and acutely ill and who was vomiting gross blood. The skin was dry, loose and sallow. There were areas of alopecia over the parietal areas of the scalp due to pre-existing fungus infection. The conjunctivas and pharynx were moderately injected. The heart and lungs were normal except for a soft systolic apical murmur, the blood pressure was 122/88. The abdomen was tense, tender and slightly distended, with marked peristaltic activity audible to the naked ear. No organs or masses were felt, owing to the marked abdominal tenderness and spasm, but on the 2nd hospital day the liver was palpated two and a half fingerbreadths below the right costal margin. There was no peripheral edema, neurologic examination was essentially negative.

Examination of the blood disclosed a red-cell count of 5,500,000, with a hemoglobin of 17.5 gm, and a white-cell count of 9850, with 89 per cent neutrophils, many of which showed toxic granulation. A specimen of urine measured 100 cc. and was grossly bloody, and gave a +++ test for albumin and a + test for sugar (following intravenous injection of glucose), the sediment was filled with degenerated red cells. The nonprotein nitrogen was 40 mg per 100 cc., and the carbon dioxide combining power 46 vol per cent. A Gettler test on the vomitus and the urine showed traces of mercury.

Eight hours after the initial ingestion of mercuric chloride — during which the patient had been given milk, cream and egg white by mouth, 2000 cc. of 5 per cent glucose in physiologic saline solution and distilled water and 1 gm of sodium

thiosulfate intravenously — a supply of BAL in oil (Dimer captopropanol, United States Army Medical Department Item 1088500<sup>16</sup>) had been obtained. The patient was given 10 per cent BAL in oil intramuscularly in the dosage recommended by Eagle and Longcope<sup>17</sup> 350 mg initially, 175 mg 2 hours later, 175 mg 4½ hours after the second dose and 175 mg at decreasing intervals for the next 4 days. He experienced a severe subjective reaction to the first injection, with headache, dryness of the lips, constriction of the chest, burning of the urethral meatus and transitory elevation of the blood pressure to 144/110. Thereafter, there was little or no subjective reaction to the injections. Within 48 hours hematemesis had ceased, and the small, frequent stools appeared to contain old, rather than fresh, blood.

During the first 12 hours in the hospital, the patient passed a total of 110 cc. of grossly bloody urine, thereafter, he passed no urine until the 7th hospital day. He was more comfortable but developed increasing azotemia, so that on the 4th hospital day, the nonprotein nitrogen was 109 mg, the blood urea nitrogen 67 mg, the serum sodium 370 mg, and the total protein 6.5 gm per 100 cc., the carbon dioxide combining power was 40 vol per cent. The cephalin-flocculation test (Hanger) was ++++ in 24 hours.

On the 5th hospital day — the 4th day of complete anuria — continuous peritoneal lavage was instituted with modified Tyrode's solution containing 2 per cent glucose, 2.9 per cent sodium bicarbonate and effective concentrations of heparin, penicillin and streptomycin. Small parallel incisions were made on the right and left lateral aspects of the abdominal wall at the level of the umbilicus, one was fitted with a stainless-steel, blunt-tipped suction nozzle for inflow, and the other with a large stainless-steel sump drain inserted well down into the pelvis, with a loosely fitting, straight suction tube laid inside the sump. Grossly bloody abdominal fluid, which gave a negative Gettler reaction for mercury, was recovered through both incisions.

The inflow and outflow tubes were fitted into the continuous-flow and suction apparatus described by Frank et al,<sup>14</sup> and as much perfusing fluid as possible was run through the abdominal cavity, depending on the rapidity with which the suction apparatus could withdraw fluid and prevent painful distention. For the first 2 days of lavage flow was satisfactory, reaching a maximum of 30 liters in the second 24 hours. Thereafter, because the patient tampered with the dressings, the inflow and outflow tubes and the regulating clamps, satisfactory perfusion was never maintained. The highest subsequent daily total was 23 liters on the fifth day, other daily rates varied from 3 to 14 liters. Peritoneal lavage was maintained as steadily as possible for 12 days, since by that time no free fluid could be aspirated through the blocked suction tube, even after removal and cleaning of the tube, lavage was discontinued.

Throughout the hospital course, supportive treatment was given with intravenous fluids, frequent transfusions and supplementary vitamins B, C and K parenterally. On the 6th hospital day a few coarse rales appeared over the left posterior lung base, the temperature gradually rose to 100°F. Penicillin given intramuscularly in doses of 20,000 units at 3-hour intervals, followed by streptomycin in doses of 0.1 gm, administered every 3 hours with the penicillin injections, caused gradual defervescence after the 11th hospital day. The patient was given deep breathing and coughing exercises, and the basal rales gradually diminished. No significant organism was found in the sputum except an apparently air-borne yeast, which was also growing in the outflow bottle of the peritoneal lavage. On the 10th hospital day, because of increasing abdominal distention and decreasing audible peristalsis, a Miller-Abbott tube was passed, this effected gradual decompression, but on the 18th hospital day the patient, while momentarily unobserved, pulled out the tube and shortly thereafter vomited small amounts of blood.

The patient voided 50 cc of clear urine on the 7th hospital day, 32 cc. on the 9th day, and daily increasing amounts thereafter, to a maximum of 910 cc. on the 26th day. The urea nitrogen content of this urine, however, never became higher than 300 to 400 mg per 100 cc., which was grossly inadequate to maintain nitrogen balance. The outflow from the peritoneal lavage contained urea nitrogen in concentrations roughly equal to those of the blood, no other chemical determinations were done on the fluid. The blood nonprotein nitrogen, which had risen to 109 mg per 100 cc. before peritoneal lavage, remained in the vicinity of 100 mg until

the 11th hospital day, when it again rose precipitously to 150 mg per 100 cc. The blood urea nitrogen at that time was 105 mg per 100 cc., the carbon dioxide combining power had remained between 20 and 40 vol. per cent by virtue of daily intravenous administration of 1/6 molar sodium lactate. When peritoneal lavage was completely discontinued azotemia increased still more rapidly on the 25th hospital day the nonprotein nitrogen was 365 mg the serum sodium 473 mg., and the potassium 21.4 mg per 100 cc. and the carbon dioxide combining power 33 vol. per cent.

On the 22nd hospital day the patient developed edema of the sacrum, scrotum and ankles further edema was forestalled by reduction of intravenous fluid to 1500 cc. daily. He rapidly failed, with increasing drowsiness continuing abdominal distention and a temperature of 97°F. On the 23rd hospital day a much louder apical systolic murmur was heard no friction rub was made out at any time. From the 24th day onward the patient vomited and defecated fresh blood, and on the 26th day he appeared irrational. On the 27th day he suddenly became cyanotic while sitting up in bed and died.

**Autopsy** At post mortem examination performed by Major Samuel Berg 6 hours after death, the abdomen was distended, there were recent surgical incisions from the insertion of tubes for peritoneal lavage. There was mild generalized edema, most marked over the prethoracic regions. The greater omentum was attached to the abdominal wall and underlying viscera by many adhesions varying from thin to firm fibrous bands. There was a large quantity of blood-tinged peritoneal fluid containing flakes of fibrin. Between many coils of intestine there were pockets of thick, yellow, odorless pus which on culture showed colonies of *Escherichia coli* and of *Monilia*. There was a well advanced "uremic pericarditis," with fibrous adhesions and 30 cc. of blood-tinged pericardial fluid.

The right lung weighed 750 gm. and the left 450 gm. The bronchi were congested there was moderate pulmonary edema, most marked in the lower lobes. There were several isolated thick walled small abscesses.

The heart weighed 490 gm., the musculature was extremely flabby. Measurements of the valves were within normal limits. The thickness of the left ventricle was 18 mm. About the chordae tendineae of the posterior cusp of the mitral valve there was a firm constricting—apparently ante-mortem—clot, with a pencil-sized tail extending upward through the aortic valve.

The spleen was normal except for mild congestion. The liver weighed 2700 gm., and was softer than normal in consistency. The pancreas was embedded in a mass of fragile fatty material. The entire lesser peritoneal sac contained 60 cc. of turbid brown fluid, with soft, whitish flakes.

Examination of the gastrointestinal tract revealed a plastic brown exudate over the posterior wall of the stomach, a perforation of the stomach had apparently occurred and had subsequently been walled over by exudate. There was marked hemoglobin staining of the mucosa of the entire intestine, the mucosa was thin and there were numerous necrotic transverse ulcerations throughout the distal duodenum, proximal jejunum and the entire colon. From the position of the ulcers and the nearby peritoneal abscesses, it was the opinion of the pathologist that perforation of the intestine had occurred in several places.

The right kidney weighed 420 gm., and the left 460 gm. When each kidney was transected the parenchyma bulged high above the cut edge of the capsule. Both kidneys were pale throughout, the glomeruli could not be visualized grossly.

The brain weighed 1270 gm. and was grossly normal. Microscopical examination disclosed that some alveoli of the lungs were partly collapsed others showed emphysematous distention. The alveolar capillaries were markedly distended and in sections from the lower lobes, the alveoli contained moderate numbers of erythrocytes and pigment-bearing phagocytes, as well as some small, round cells. There was marked disparity in the size of the cell nuclei of the liver. The cytoplasm was finely granular, and in places there were large, round vacuoles suggesting fatty degeneration. Many of the hepatic cells and a few of the Kupffer cells were almost filled with light-brown pigment granules. There were moderate numbers of small round cells about the bile ducts and in foci in the capsule of Gerson. There was extensive necrosis of the peripancreatic tissue, without changes in the pancreatic tissue itself.

The glomerular tufts of the kidneys were anemic and showed edema and desquamation of the capsule epithelial cells but were otherwise normal. The tubules showed marked changes, with no uniformity from place to place. The epithelial cells were loosely attached to the basement membrane, with some cells lying free in the lumens. Some of the tubules singly and in groups, showed marked atrophic changes, the few epithelial cells lying haphazardly in clusters within an edematous stroma containing small round cells and a few polymorphonuclear leukocytes. In a few places in the distal tubules on the other hand, the epithelial cells were stratified and the nuclei varied in size, suggesting recent regeneration.

In this case peritoneal lavage was used in an attempt to maintain life for a sufficient period to allow restoration of kidney function after sudden failure. Despite survival for twenty-seven days, it is evident that sufficient kidney function had not been restored in that time to sustain nitrogen balance unaided, since although a urinary volume of 910 cc was achieved on the last day of life, there was not adequate concentration to ensure removal of large amounts of uremic metabolites from the body. It is certain, however, that the procedure of peritoneal lavage prolonged the patient's life at least ten to fourteen days beyond the expected survival period in complete anuria. Despite the optimistic figures given by Eagle and Longcope,<sup>17</sup> treatment with intramuscular BAL did not appear to effect significant detoxification of the ingested mercury, since the drug could not be obtained until eight hours after the onset of poisoning, it is possible that administration at an earlier time in the illness would have been more effective.

The difficulty in maintaining free flow in peritoneal lavage in this case is best explained, in retrospect, by the supervention of sepsis and adhesions in the abdomen. It is believed that the patient's lack of co-operation in tampering with the apparatus and skin incisions had much to do with this situation, the likelihood of air-borne contamination around the outflow suction, the undecided influence of intestinal perforation and the ever-present possibility of contamination during manipulations of the apparatus, which were not carried out under operating-room asepsis, must also be borne in mind. Again, the patient's summary removal of the Miller-Abbott tube undoubtedly aided in increasing intra-abdominal pressure, which constituted another interference with free intraperitoneal flow.

On the basis of this experience it seems that peritoneal infection is a danger that, as stated by other authors, must be taken into consideration but need not be considered a barrier to institution of this therapy in cases that can be suitably controlled. On the contrary, the survival of this anuric patient for twenty-seven days is regarded as an encouraging result pointing to a better prognosis in similar cases handled with improved technic.

#### SUMMARY

The literature pertaining to treatment of acute uremia by peritoneal lavage is reviewed.

A case is reported in which continuous peritoneal lavage for twelve days resulted in survival for twenty-six days after complete renal shutdown due to mercuric chloride poisoning.

The importance of avoiding peritoneal infection in this procedure is stressed, but further evidence is added for the growing opinion that "substitution" for the nonfunctioning kidneys in acute uremia is a practicable and useful procedure.

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## MEDICAL PROGRESS

### HEMATOLOGY\*

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THIS report covers recent progress in the investigation and treatment of the anemias and the hemorrhagic diseases.

#### ANEMIAS

As in previous progress reports, the anemias are classified primarily on etiologic grounds. Such a classification is simple and easily remembered and may be said to be based on economic principles: the bone-marrow "factory" requires materials for the production of its most important finished product, the red cell. Anemia results when the materials necessary for supplying the bone-marrow factories are inadequate, the factories themselves are inadequate or there is an excessive loss either by hemorrhage or by increased breakdown of the finished product, the red cell. Stated in more conventional scientific terms the anemias may be classified as due to deficiency of materials, bone-marrow disturbances and excessive blood loss, whether hemorrhagic or hemolytic.

#### Deficiency Anemias

**Folic acid.** The outstanding advance of the year is undoubtedly the advent of folic acid as a therapeutic agent in deficiency syndromes associated with macrocytosis of the red cells.

The devious routes by which folic acid came into being as a drug that the medical practitioner could use in his daily practice are fully described in a comprehensive article by Berry and Spies.<sup>1</sup> The apparently dull and impractical researches of bacteriologists, nutritionists, chemists and other "pure" scientists finally led to the development of a highly potent agent that, in a dosage of a few milligrams a day, was sufficient to result in remissions in pernicious anemia, sprue and related conditions.

The lowly bacterium, more particularly the *Lactobacillus casei*, provided the test subject for various growth factors, which could then be methodically studied. Snell and Peterson<sup>2</sup> found that these bacteria required extracts of plants or animals for proper growth. Yeast extract and certain fractions of liver extract were both rich sources of the essential growth factor, or the *L. casei* factor as it came to be called. Patient fractionation finally yielded a relatively simple material that was present in high concentration in spinach, a leafy vegetable—hence the term "folic acid." The pure compound was seventy-five to one hundred and thirty-seven thousand times as active as a standard liver fraction.

Since 1932 Wills and Bilimoria<sup>3</sup> had been working on a type of anemia that could be produced in monkeys by a diet similar to that consumed by

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certain Indian natives This anemia, which was macrocytic in type, could be prevented or cured by a crude autolyzed yeast extract or by Cohn's liver extract, fraction G The exact vitamin responsible could not be determined but was called vitamin M When the *L casei* factor became available, it was used in the deficient monkeys and resulted in a dramatic return to normal of all evidences of the deficiency state, including the abnormal blood picture Other investigators, often working in large teams (fifteen authors are listed in one article), attacked the problem of certain deficiency states in chicks in which a macrocytic hyperchromic anemia was present<sup>4</sup> Prevention and cure of this deficiency was finally achieved by a fraction of the vitamin B complex The exact nature of this material, which was called the vitamin B<sub>12</sub> factor (vitamin B<sub>12</sub>, chick factor) could not at first be determined, but work by other groups demonstrated that effects identical with those induced by the vitamin B<sub>12</sub> factor could be duplicated by the use of the *L casei* factor Conversely, the vitamin B<sub>12</sub> factor replaced the *L casei* growth factor in experimental work with *L casei* Synthesis of the material, which was called pteroylglutamic acid, was finally achieved by a group of chemists working in the Lederle Laboratories,<sup>4</sup> and it was then determined that this new compound was equally effective in the deficiency anemia of chicks, the M deficiency state of monkeys and the *L casei* nutritional deficiency of bacteria

The folic acid material, which was extracted from previously discarded liver-extract residues, was chemically analyzed and later synthesized and was then supplied to a number of investigators interested in nutritional problems Among these was Spies,<sup>4</sup> whose investigations in pellagra and in other deficiencies involving the vitamin B complex had been outstanding Spies and his collaborators had previously tried, with relatively little success, fractions of the vitamin B complex in certain cases of anemia, which were usually of the macrocytic type With the use of the newly synthesized folic acid striking clinical and hematologic effects were obtained<sup>6-11</sup> The hematologic response, which was considered to be identical with that found in pernicious anemia when liver extract was given, showed a reticulocytosis with a subsequent rise in red cells, hemoglobin and leukocytes These results were quickly confirmed by various observers, including Moore and his associates,<sup>12</sup> who reported clinical and hematologic remissions in 2 patients with pernicious anemia after the daily oral administration for ten days of 30 mg and 100 mg, respectively, of the synthetic material A patient with the macrocytic anemia of nontropical sprue and another with pernicious anemia of pregnancy responded similarly when given the material intravenously in a dosage of 20 mg Zuelzer and Ogden<sup>13</sup> showed that folic acid was also effective in the treatment of the

megaloblastic anemia of infancy These cases, which presented pallor, vomiting, fever, slight cardiac enlargement and, at times, splenomegaly, demonstrated a normochromic, macrocytic blood picture and a megaloblastic bone marrow Folic acid resulted in reticulocytosis, erythrocytosis and a return of the bone marrow to normal

Numerous reports have since appeared from various parts of the country and have shown conclusively that 5 to 20 mg of folic acid given orally as a daily dose is sufficient to induce a well marked, often maximal, reticulocytosis and a well defined, if not maximal, erythrocytosis Simultaneously, striking responses take place clinically It is not yet completely settled whether folic acid causes consistently maximal responses in erythrocytes similar to those produced by liver extract, or whether folic acid alone prevents or improves the neurologic lesions of pernicious anemia More theoretical questions are discussed below Watson and Castle<sup>14</sup> demonstrated the effectiveness of a material other than pure liver in certain cases of "nutritional macrocytic anemia," especially in pregnancy These cases had failed to respond to the parenteral administration of refined liver extract in doses ordinarily sufficient to induce a remission in ordinary cases of pernicious anemia, but when a crude oral extract of liver (Valentine) was given, excellent responses occurred Unfortunately, sufficiently large doses of folic acid were not given to these patients to determine whether they would have responded to this medication The observations are nevertheless of great importance as indicative of the fact that nutritional macrocytic anemias may be of various types some responding to pure liver extract, some responding to folic acid but not to pure liver extract, and some responding to either material (and perhaps some responding to neither)

Spies and his co-workers demonstrated that folic acid was effective in all the deficiency states associated with a macrocytic anemia These included not only pernicious anemia but also certain cases of vitamin B complex deficiency Sprue seemed to be a condition in which this material could well be effective The favorable response of a few cases of nontropical sprue to folic acid had already been noted by Moore et al<sup>12</sup> and by Darby and Jones<sup>15</sup> In Cuba, Spies and his associates<sup>9, 10</sup> quickly collected a group of cases of tropical sprue treated with folic acid Preliminary observations by Spies and his co-workers<sup>9</sup> and later by Spies and Suarez<sup>16</sup> in Puerto Rico demonstrated that small doses of material (5 to 15 mg daily by mouth) usually resulted in dramatic clinical and hematologic improvement, this was often far greater than that obtained by the use of large doses of crude liver extract in association with a well balanced diet

The synthesis of folic acid was a difficult chemical task and was undertaken by a large group of

chemists working in the Lederle Laboratories. Although synthesis was first announced in 1945, the actual details of chemical identification and methods were kept secret until approximately a year later, when a publication by Angier and his collaborators<sup>4</sup> appeared. Chemically, folic acid consists of a substituted pteridine combined with a molecule of para-aminobenzoic acid and a molecule of glutamic acid to which the name "pteroylglutamic acid" was applied.

The theoretical aspects of folic acid therapy resulted in a whole new set of problems to plague the investigator especially at a time when it seemed that the problem of pernicious anemia was to a great extent solved or at least quiescent. The response to two entirely different substances is puzzling. Castle's theory of the interaction of an "extrinsic" factor in the food with an "intrinsic factor" in the gastric juice leading to the development of a "liver-extract factor" or an "erythrocyte-maturation factor" is by no means invalidated. Folic acid appears to be neither the extrinsic nor the intrinsic factor. Heinle<sup>17</sup> discusses these theoretical matters at length. On the basis of preliminary experimental data, he concludes that a "principle of liver extract, possibly the antipernicious anemia factor is concerned with the release of free folic acid from conjugates of the vitamin." This would, of course, explain the identical action of two distinctly different substances, patients with pernicious anemia, although they might possess adequate amounts of conjugated folic acid would find it of little value because free folic acid could not be liberated. Liver extract apparently releases this material from the conjugated substance, and folic acid, of course, supplies it ready made. In a review of the clinical and experimental aspects of folic acid, Doan<sup>18, 19</sup> makes the point that this material is essential for normal cellular metabolism, lacking it, the marrow becomes defective with resulting pernicious anemia. Perhaps to confuse the picture even more for the ordinary reader is the report by Spies and his co-workers<sup>20, 21</sup> on the antianemic properties of thymine. This material, which is derived from thymonucleic acid, was also effective (in massive doses of 4.5 to 15 gm daily) in causing remissions in pernicious anemia. The relation of this material to folic acid is quite obscure, although Spies and his collaborators suggest that the latter substance acts as an enzyme or coenzyme in the synthesis of thymine or a thymine-like material.

*Other aspects of pernicious anemia.* The following papers deal with didactic matters that, in comparison with the dramatic events relating to folic acid therapy, seem relatively dull. Schwartz and Rappolt<sup>22</sup> report 3 cases of pernicious anemia in Chinese hospitalized at the Cook County Hospital. Another case in a Chinese is reported by Hartwell<sup>23</sup> from Honolulu. The occurrence of carcinoma of the esophagus in a long-established case of perni-

cious anemia is described by Cooke,<sup>24</sup> and that of leiomyosarcoma of the stomach by Schindler and his associates.<sup>25</sup> Typical examples of the disease occurring in children are described by Jonssen<sup>26</sup> and by Peterson and Dunn,<sup>27</sup> as well as by Zuelzer and Ogden.<sup>13</sup> The following criteria should be present: macrocytic anemia, histamine-resistant achlorhydria, megaloblastic marrow, reticulocytosis after liver-extract therapy and necessity for continued administration of liver extract. The occurrence of pernicious anemia in association with intestinal strictures and anastomosis is discussed by Richardson,<sup>28</sup> who believes that a stagnant intestinal loop, by causing damage to the intestinal mucosa, helps to bring about the disease. A likelier explanation is that malabsorption of the liver-extract factor results in a conditioned deficiency of this substance.

Cayer, Ruffin and Perlzweig<sup>29-31</sup> studied the levels of various vitamins in the disease. Those of vitamin A and pyridoxin were within normal limits in all patients, but those of niacin (nicotinic acid), riboflavin and thiamine were below normal. The authors concluded that, if liver extract alone does not result in a completely adequate response in pernicious anemia, components of the vitamin B complex should be given. (This is even more applicable to folic acid, a fraction of the vitamin B complex.)

Liver-extract sensitivity not infrequently develops in the course of parenteral therapy. In a large series of cases treated at the Cook County Hospital in Chicago, Schwartz and Legere<sup>32</sup> found that 17 per cent of patients developed manifestations of sensitivity including itching, flushing, tachycardia, asthmatic reaction or even shock. Treatment of this sensitivity is relatively easy in most cases and consists in a change of the brand of extract, particularly to one in which beef liver is used instead of the pork product, reduction of the dose of material and desensitization, which is often unsatisfactory. In stubborn cases Schwartz suggests the use of a histamine protein complex to produce antihistamine antibodies, with the use of this "anti-H" material\* good results were obtained in 10 of 11 cases. Folic acid has naturally revolutionized the treatment of desensitization.

The neurologic complications of pernicious anemia are in some ways far more important than the hematologic — and far less readily controlled. Although disorders due to disturbances of the posterolateral column of the spinal cord are best known, Rundles<sup>33</sup> points out that three other types of involvement may occur: cerebral, olfactory and that of the peripheral nerves and nerve roots. Olfactory symptoms were found in 4 of 20 cases, perversion or loss of taste for foods, especially for proteins, occurred independently of atrophic or inflammatory changes of the lingual mucosa. Eleven of the 20 patients had involvement of the peripheral nerves.

\*Obtainable from Parke, Davis and Company of Detroit

as well as of the posterior columns of the spinal cord. Foster<sup>34</sup> also points out the importance of peripheral-nerve involvement in pernicious anemia. Although it is clinically difficult to distinguish involvement of the posterior column from that of the peripheral nerve, it is essential to give maximum therapy, since peripheral nerves have a marked regenerative capacity and may thus be influenced by treatment.

Large doses of liver extract are recommended to combat the neurologic disorder, 30 to 60 units of concentrated extract being given weekly by parenteral injection until a maximum neurologic response has been obtained. Although the degree of remission cannot be foretold, one can be certain that with the continued use of about 15 units of extract every ten to fourteen days, no neurologic relapse will occur.

**Iron-deficiency anemia.** Schwartz and Flowers<sup>35</sup> describe the changes in the blood that occur in the course of gradually developing chronic iron deficiency, usually owing to chronic bleeding. There is a linear fall in the hemoglobin, with the red-cell count constantly lagging behind and resulting in an ever-decreasing color index. As this diminishes, characteristic changes in the red cells develop: microcytosis, hypochromia, anisocytosis and poikilocytosis. Recognition of the iron-deficiency state is important, since liver extract is of no value. Although therapy with iron salts may be effective, a search for an etiologic factor must be made. Goetsch, Moore and Minnich<sup>36</sup> describe the effects of massive doses of iron intravenously in patients with hypochromic anemia. Although the reticulocyte response is often higher and the average rate of hemoglobin regeneration greater than with oral therapy, toxic reactions are frequent and severe and thus militate against the use of this therapy in clinical practice.

The use of molybdenum in combination with iron in the treatment of iron deficiency is described by Neary<sup>37</sup> and Healy<sup>38</sup>. Molybdenum, a so-called "trace element," was first used in the milk-induced anemia of rats. Neary studied 22 patients with iron deficiency of pregnancy, of whom half received ferrous sulfate alone, and half molybdenum ferrous sulfate. The patients receiving the latter combination showed a more rapid therapeutic response. Healy stated that the response to molybdenum was striking, with an average daily increase in hemoglobin of 0.36 gm per 100 cc, whereas with iron alone, in comparable cases, the average increment was only 0.12 gm per 100 cc. The results in both these papers are subject to further critical evaluation.

Schulze and Morgan<sup>39</sup> found that the addition of ascorbic acid to iron was valueless in the therapy of iron-deficiency anemia of children. It may be added parenthetically that in the presence of a state of iron deficiency, iron alone is usually all that is required for therapy. It is highly questionable whether liver extract, folic acid, copper, molybdenum and vitamins of various types do anything

except add to the cost of the preparation. Another more serious danger in the treatment of iron deficiency results from the treatment of the anemia as such, rather than finding out, first of all, what the underlying cause may be. I have seen a number of cases of hypochromic anemia in which prolonged therapy (usually with liver extract) was given but in which examination of the stools later demonstrated strong reactions for occult blood and x-ray films of the gastrointestinal tract demonstrated a bleeding lesion, usually cancer. In every case of hypochromic anemia of obscure etiology, it is imperative to search for a bleeding lesion. Diaphragmatic hernia is occasionally found, as pointed out by Chevallier and Danel<sup>40</sup>. These authors, however, suggest that the anemia is due to an inflammatory disturbance of the gastric mucosa. In the cases that I have observed, occult blood has always been demonstrated, provided enough stools were examined. In some cases brisk or constant bleeding is present.

#### *Bone-Marrow Anemias*

Bone-marrow disturbances are usually associated with a pancytopenia — that is, reduction in red cells, white cells (granulocytes) and platelets. They are brought about by diminished growth in the marrow (hypoplasia or aplasia), by foreign-tissue infiltration or proliferation (leukemia, neoplasm or sclerosis) or by splenic inhibition in certain conditions, usually splenomegaly.

**Aplastic and hypoplastic anemia.** Quinacrine (Atabrine) as a possible cause of various types of bone-marrow disturbances was suspected during the war, but for obvious reasons such suspicions were not publicized. Custer<sup>41</sup> reports 57 cases of aplastic anemia in soldiers from the Pacific and the China and India-Burma theaters. Although the Army personnel in these areas was only one twenty-fifth to one seventh of the total troop strength, two and a half times as many cases of aplastic anemia appeared as in soldiers from the European Theater. Quinacrine was used by a large portion of the personnel in the Pacific and the China and India-Burma theaters, and, in addition to anemia, dermatitis, weakness and hemorrhagic disturbances were noted. Most and Hayman<sup>42</sup> report a single case of quinacrine aplastic anemia. A report by Greenfield<sup>43</sup> on aplastic anemia that was thought to be due to a "rifle-bore cleaner" is of interest in that quinacrine had also been used by the patient.

New medications containing the benzene ring suggest new causes for aplasia or hypoplasia of the bone marrow. Tridione, which was recently introduced as an anticonvulsant drug, has been implicated in cases reported by Harrison, Johnson and Ayer<sup>44</sup> and by Mackay and Gottstein<sup>45</sup>. Other chemical agents recently implicated in the production of aplastic anemia include the sulfonamides (Denny and Menten<sup>46</sup>), trinitrotoluol (Sievers,

Stump and Monaco<sup>47, 48</sup>), Stovarsol (Schrire<sup>49</sup>), calcium bisulfite (Carlson<sup>50</sup>), estradiol benzoate — estrogen (Chevallier and Umdenstock<sup>51</sup>) and benzene (Aubert<sup>52</sup>). Although some of the reports are not convincing regarding a direct relation of the chemical to the aplasia, it is important to record even possibilities, since this is a chemical age and potentially dangerous materials must be guarded against. It should also be pointed out that some cases of aplastic anemia, particularly in children, are probably largely congenital in origin and become definitely evident only after a drug such as sulfadiazine has been given. The Nagasaki and Hiroshima atomic bomb explosions led to countless cases of radiation sickness. Death followed in most cases, but patients who were relatively slightly affected developed varying degrees of bone-marrow involvement. One of the first articles on this subject dealing principally with the clinical effects noted is that of Timmes<sup>53</sup>. Pancytopenia was present in most cases but in others "selective" cytopenias were present, including extreme granulocytopenia, thrombocytopenia and anemia. Lack of facilities made therapy difficult, thus, only rare cases received transfusions of blood and penicillin. Hemorrhage from lack of platelets and uncontrolled infection from agranulocytosis were frequently observed. In the mildest cases the patients recovered. It will be of interest for future investigation to note whether leukemia or other leukocytic proliferations occur in greater incidence in persons exposed to the atomic bomb than in other groups. The therapy of aplastic anemia is extremely difficult and often of no avail. Folic acid has been used by Denny and Menten<sup>46</sup> and by Peat<sup>54</sup> with questionable results. I have seen favorable results from splenectomy in the congenital hypoplastic anemia of children, and this procedure should be seriously considered, particularly if megakaryocytes are not completely lacking. Splenectomy apparently removes a normal inhibitory or regulatory influence on the bone marrow and thus allows more marked red-cell, white-cell and platelet production to take place than would otherwise occur.

#### *Anemias Associated with Increased Blood Destruction*

The anemias of increased blood loss may be either hemorrhagic or hemolytic. The former are of chief importance from the standpoint of diagnosis, particularly in the presence of continued slight bleeding from the gastrointestinal tract. The latter anemias are assuming an ever-increasing significance as more and more cases are being recognized. They may be classified as follows: the familial and hereditary, including the spherocytic, target-oval (Mediterranean) and target-sickle (sickle-cell) types, the acquired, comprising the acute, subacute and chronic, those caused by infections, chemicals, toxins and parasites (of known etiology), those associated with leukemia, lymphoma, Hodgkin's disease and

so forth (symptomatic), those associated with iso-antibodies, such as hemolysins and agglutinins and the hypersplenic type, and the hemoglobinurias.

**Familial types** The familial and hereditary hemolytic anemias are for the most part readily differentiated according to the predominating type of red cell picture. The spherocytic type is the best known and is associated with the presence of small, thick dense-appearing red cells, which have an increased fragility in solutions of hypotonic sodium chloride. Several investigators have shown that the red cells of this disease have a diminished life span in a normal circulation, when the spleen is removed, the life span of the spherocyte is normal. The cause of the spherocytosis is unknown. Most authorities consider that the spherocyte is produced by an abnormally functioning marrow. This reasoning is confirmed by two findings: blood introduced into the circulation in a case of familial spherocytosis survives at a normal rate — that is, there is no vascular hemolytic factor, and tests of the red cells with an antiglobulin serum (Boorman, Dodd and Loutit<sup>55</sup>) fail to show the presence of adsorbed antibody. Dameshek and Schwartz<sup>56</sup>, on the other hand, contend that since spherocytosis can be experimentally produced and since this abnormality indicates a red cell in the process of hemolytic destruction, a hemolytic substance is somewhere present, whether demonstrable or not. They cite other evidence. It is also possible that hemolysin or agglutinin is specific for the patient's own cells and thus does not cause increased destruction of introduced red cells. These hypotheses are being studied. The hemolytic crisis, which is associated with greatly increased spherocytosis and which may develop at any time in the course of the disease, may indicate an extrinsic factor or an accentuation of the already existing cause of the spherocytosis. Familial crises are reported by Horne et al.<sup>57</sup> and have previously been observed by Dedichen<sup>58</sup> and Dameshek.<sup>59</sup> In the cases presented by Horne and his associates the red cells contained peculiar inclusion bodies that were perhaps related to Howell-Jolly bodies.

The various clinical types of the target-cell and oval-cell syndromes, which occur primarily in persons of Mediterranean ancestry, have been reported by Dameshek.<sup>60</sup> All cases show target, oval and stippled cells and increased hypotonic resistance of the red cells. A typical mild case with hypochromic erythrocytosis occurring in a Chinese is reported by Greenblatt, Cohn and Deutsch.<sup>61</sup> Stiles, Manlove and Dangerfield<sup>62</sup> presented a characteristic case in a Negro in whom there was complete absence of sickling. Another probable case in a Negro is reported by Faber and Roth.<sup>63</sup> Two cases occurred in Palestine in Bucharan Jews whose ancestors had lived for perhaps a thousand years on the shores of the Caspian Sea.<sup>64</sup> Another case is reported from

South Africa in a European of German and French origin<sup>66</sup>

The mild cases of Mediterranean syndrome have no great significance, except that they represent carriers of a trait that is transmitted in a Mendelian-dominant fashion. Two affected carriers may beget children with the fatal Cooley's anemia, the severest form of this disease. Mild and moderately severe cases are often mistaken for iron-deficiency anemia, lead poisoning, spherocytic hemolytic anemia and even polycythemia. No satisfactory therapy has as yet been established.

Sickle-cell disease, which is largely present in people of African stock, may occur in persons of Mediterranean origin. Sickle-cell anemia with ankle ulcers is reported in a white brother and sister<sup>68</sup>. The sickle-cell trait is noted on the average in 7 to 8 per cent of Negroes. In 5500 West Africans, Findlay, Robertson and Zacharias<sup>67</sup> found an incidence of 12.5 per cent sickling. Of 403 South African Bantus, however, Altmann<sup>68</sup> observed only 0.25 per cent with sickling. In the United States Army, Henderson and Thornell<sup>70</sup> reported a 7 per cent incidence of the trait. It is of interest that, under conditions of lowered arterial oxygen tension, none of the patients showed intravascular sickling or increased hemolysis.

Ponder<sup>71</sup> studied the highly interesting question of how and why the red cell sickles under conditions of reduced oxygen tension, and his paper should be read in the original by those who are interested. The pathogenesis of the development of thrombotic manifestations in sickle-cell anemia is discussed by Murphy and Shapiro<sup>72</sup>. The red cells, under conditions of anoxemia, become rigid, producing mechanical impaction and eventually resulting in slowing of blood flow and thrombosis. The cardiovascular lesions of sickle-cell disease are described by Wintrobe<sup>73</sup>. Two cases—one of them fatal—of sickle-cell anemia complicated by pregnancy are reported by Noyes<sup>74</sup> and by Zimring<sup>75</sup>. In the latter case, there was acute illness, pallor and jaundice during labor.

Two new familial hemolytic syndromes have been described in the past year. Rundles and Falls<sup>76</sup> report a hypochromic, microcytic anemia occurring in association with splenomegaly, increased hypotonic resistance of the red cells and failure to respond to splenectomy. Although in many respects the cases resemble those with Mediterranean anemia, no evidence of Mediterranean ancestry was present. Stransky and Regala<sup>77</sup> describe 4 cases of hemolytic anemia in 5 Filipino siblings. There was no spherocytosis or leptocytosis, but many nucleated red cells were present. Splenectomy was without effect in 3 cases.

*Acquired types.* Ross and Paegel<sup>8</sup> present the case of a four-year-old child who developed an extremely severe acute hemolytic anemia with hemoglobinuria after the administration of a small

amount of sulfadiazine. Hypersensitivity to this drug had probably occurred as the result of two previous administrations. Improvement did not occur until a vein was cannulated and large amounts of blood (1100 cc.) given over a period of eight hours. Cockett<sup>78</sup> describes the case of a young man who received benzyl-sulfanilamide as a prophylaxis for minor second-degree burns of the legs. Three days later, after 17 gm had been given, weakness, loin pains, hematuria and severe hemolytic anemia developed. Recovery ensued after the administration of two transfusions of blood. Young, Valentine and Howland<sup>80</sup> report the first case of acute hemolysis following the injection of neoarsphenamine. A previous injection of the drug had caused nausea and vomiting. Five minutes after the second injection the patient developed severe symptoms and died within twenty-four hours. Autopsy showed hemoglobinuria, icterus, spherocytosis and normoblastosis.

Jope<sup>81</sup> studied the disappearance of sulfmethemoglobin in 7 cyanotic trinitrothrene workers who had developed sulfhemoglobinemia. The abnormal hemoglobin compound was retained within the affected red cell until its destruction, which occurred on the average in one hundred and sixteen days. This period may be considered the life span of the red cell containing sulfhemoglobin.

The development of isoantibodies (hemolysins or agglutinins) within the body may result in auto-hemolysis and thus in hemolytic anemia. Finland et al.<sup>82</sup> found hemolytic anemia in 11 of 200 cases of primary atypical pneumonia. This usually occurred when the maximal titers of cold hemagglutinin were present and was apparently independent of sulfonamide therapy. With marked cold auto-agglutination, there was usually a wide thermal range, so that hemolysis could occur within the circulation as the result of agglutination, which results in increased mechanical fragility. A more general article on the clinical significance of cold hemagglutinins is that of Young<sup>83</sup>. Lubinski and Goldbloom<sup>84</sup> report a fatal case of hemolytic anemia in which the cold hemagglutinin had a wide thermal amplitude and was active to some extent at incubator temperature. Boorman and his associates<sup>85</sup> consider some of the mechanisms by which cold hemagglutinins may become activated to produce hemolysis in the circulation even at 37°C. Cases showing abnormal isoantibodies, either agglutinins or hemolysins, require special consideration when transfusions are contemplated. As stated above antibodies are adsorbed to the red cells in some cases and are not found in the serum. Boorman, Dodd and Loutit<sup>86</sup> demonstrated adsorbed agglutinin in a series of cases of idiopathic acquired hemolytic anemia by testing the red cells with antihuman globulin rabbit serum. Adsorbed antibody was not demonstrated in familial spherocytosis.



Transfusions and splenectomy remain the chief therapeutic agents in hemolytic anemia. Transfusions alone are rarely effective except in cases due to chemical poisoning and in those due to parasites (malaria and Oroya fever). Splenectomy must be resorted to in many cases, particularly when transfusions have been ineffectual. An excellent prognosis can be promised in familial spherocytosis, but in the acquired hemolytic cases, the outlook is not entirely certain. About 7 of 10 patients do well after splenectomy, but the others are either partially or only slightly benefited, if at all. Attempts to diminish red-cell destruction by a diet low in fat have proved ineffective (Evans<sup>86</sup>). Rare patients with refractory hemolytic anemia have recovered after the removal of an ovarian tumor (Singer and Dameshek<sup>87</sup> and Jones and Tillman<sup>88</sup>). Penicillin therapy was used with a favorable effect by Merino<sup>89</sup> in a case of human bartonellosis.

### Anemia of Infection

Infection causes disturbances in red-cell development in the bone marrow. Such cases have been studied extensively in Wintrobe's laboratory and reported on in a series of articles by Cartwright and his collaborators.<sup>90</sup> It was found that a reduction in serum iron, an increase in serum copper, an increase in erythrocyte protoporphyrin and an increase in coproporphyrin output in the urine were present. The serum bilirubin and urobilinogen excretion were normal and thus indicated that hemolysis was not a factor. The red cells were normocytic and normochromic. The anemia failed to respond to iron (oral or intravenous), copper, components of the vitamin B complex, ascorbic acid, Amigen, globin, cystin, methionine or crude liver therapy. Indications of an altered iron metabolism were present, the iron being diverted from the marrow to the tissues and thus being made unavailable for hemoglobin synthesis.

(To be concluded)

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## NEW HAMPSHIRE MEDICAL SOCIETY

PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-SIXTH  
ANNIVERSARY

House of Delegates, June 18, 19 and 20, 1947

THE House of Delegates convened at the Wentworth Hotel, Newcastle, on June 18, 1947, at 7 30 p m, with Speaker Leslie K Sycamore presiding

The following members answered the roll call

The President, *ex-officio*  
The Vice-President, *ex-officio*  
The Secretary-Treasurer, *ex-officio*  
Samuel Feiner, Ashland  
Nathan Brody, Laconia  
W J Paul Dye, Wolfeboro  
Francis J C Dube, Center Ossipee  
Albert C Johnston, Keene  
James N Ballou, Keene  
Marjorie B Parsons, Colebrook  
Joseph E LaRochelle, Gorham (alternate for Francis M Appleton)  
Israel A Dinerman, Canaan  
Leslie K Sycamore, Hanover  
Leslie E McKinlay, North Haverhill  
Clarence E Dunbar, Manchester  
Daniel J Sullivan, Nashua  
Samuel Fraser, New Boston  
Loren F Richards, Nashua  
Robert R Rix, Manchester  
Philip M L Forsberg, Concord  
Andrew L MacMillan, Concord  
Francis Brown, Henniker  
John W Blaisdell, Epping  
Donald W Leonard, Exeter  
Fred Fernald, Nottingham  
Raymond R Perreault, Rochester  
Daniel F McCooey, Dover  
Donald C Moriarty, Newport  
B Read Lewin, Claremont  
George C Wilkins, Manchester  
Samuel T Ladd, Portsmouth  
Deering G Smith, Nashua

The Speaker declared a quorum present, and appointed the Credentials Committee as follows Drs Johnston, Moriarty and Dube

On motion duly made and seconded, it was voted to omit the reading of the previous minutes, because of the publication of the proceedings

On motion duly made and seconded, it was voted to dispense with the reading of the reports of the councilors, since they will be published in the *Transactions*

To the Committee on Officers' Reports, the Speaker appointed Andrew L MacMillan, of Concord (chairman), and Loren F Richards, of Nashua, and Donald W Leonard, of Exeter To the Committee on Memorials, he appointed Raymond R Perreault, of Rochester, Clarence E Dunbar, of Manchester, and B Read Lewin, of Claremont To the Committee on Nominations, he appointed W J Paul Dye, of Wolfeboro (chairman), Samuel Feiner, of Ashland, Joseph E LaRochelle and Robert R Rix, of Manchester, and Israel A Dinerman, of Canaan

The Secretary-Treasurer, Dr Carleton R Metcalf, presented his report, as follows

The total membership on December 31, 1945, was 528, that on December 31, 1946, was as follows

PAID	
Belknap County	32
Carroll County	16
Cheshire County	33
Coos County	33
Grafton County	69
Hillsborough County	159
Merrimack County	77
Rockingham County	55
Strafford County	39
Sullivan County	18
State members	3
	— 534
UNPAID	
Life members	18
Honorary members	5
	— 23
	557

FINANCIAL STATEMENT	
RECEIPTS	
January 1, 1946 — balance forward	\$107 24
Belknap County	168 00
Carroll County	90 00
Cheshire County	256 00
Coos County	162 00
Grafton County	352 00
Hillsborough County	852 00
Merrimack County	442 00
Rockingham County	318 00
Sullivan County	118 00
Strafford County	217 00
Cash received at annual meeting	73 00
Checks received at annual meeting	14 00
Members not in county society	18 00
Donations to National Physicians Committee	235 00
(Strafford County, \$34 Belknap County, \$28 Hillsborough County, \$123, Merrimack County, \$50 00)	80 00
Benevolence Fund	
(Rockingham County Auxiliary, \$40 Strafford County Auxiliary 1945-46 \$20 Merrimack County Auxiliary, \$20)	500 00
General Fund — Trustees	85 03
Receipts, 1945 annual meeting	
	\$4087 32

EXPENDITURES	
<i>New England Journal of Medicine</i>	\$515 49
Journals	3 10
Tabular material	500 00
Carleton R Metcalf (salary)	164 71
Printing	56 00
Envelopes and stamps	55 54
Half-tone cuts	155 50
Clerical work	33 99
Telephone and telegraph calls	100 00
Retaining fee	85 01
Guest speakers (fees)	60 00
Cancer Committee	60 00
Dues collected at annual meeting	
Benevolence Fund	40 00
Rockingham County	20 00
Strafford County	20 00
Merrimack County	
National Physicians Committee (donations)	34 00
Strafford County	28 00
Belknap County	123 00
Hillsborough County	50 00
Merrimack County	301 19
Madeline A May (stenographer at annual meeting)	162 45
Committee lunches	200 00
New England Medical Council	
Deering G Smith (expenses as delegate to American Medical Association, 1945-46)	691 89
Deering G Smith, Committee in Medical Preparedness	152 93
Auditor, trustees books	10 00
Refund on dues	12 00
Service charges at bank	2 39
	\$3657 22
	430 10
	\$4087 32
Balance January 1 1947	

Although no money was added to the Benevolence Fund from the annual dues during 1946 donations totaling \$80 were received from the auxiliaries of Rockingham County Strafford County and Merrimack County.

In accordance with instructions from the House of Delegates \$60 was given to the Cancer Committee. The number of members on this committee was increased to five.

The Committee on Mental Hygiene was asked to formulate a definite program for outpatient psychiatric care and to report at this meeting.

A year ago a National Emergency Committee was formed consisting of five men who served in the recent war. This committee was asked to consider the service of doctors in the war with the thought that in a future emergency a more efficient plan for medical care could be invoked.

The New Hampshire Board of Health has asked us to form a Committee on Industrial Health and the Committee on Rural Medical Service of the American Medical Association has asked us to form a Committee on Rural Medical Service. Both suggestions have been referred to the speaker of the House of Delegates.

The sum of \$100 was provided for our share in the Council of the New England State Medical Societies. The several meetings of this council were beneficial to New Hampshire, and it is recommended that \$100 be donated to the Council so that we may maintain our membership.

All members of the Society were notified that they could have all issues of the *New England Journal of Medicine* by sending \$1.50 a year directly to the *Journal* and all county societies were notified of the amendment to the By laws that changed the phrase "affiliate member" to "life member."

The Board of Health was informed that in the opinion of the House of Delegates health conditions in restaurants and hotels are lax and should be corrected. This alleged laxity is apparently due to an appropriation from the General Court that does not permit the employment of sufficient inspectors.

The New Hampshire Hospital Association was advised that, in the opinion of the House of Delegates routine chest x-ray examination of patients entering New Hampshire hospitals was a worthy procedure.

The New Hampshire Board of Welfare was requested to send a copy of the present fee table to every member of the Society and was informed that the fee allowances of the Blue Shield would be appropriate for indigent patients who are under the supervision of the Welfare Department.

The annual dues of the Society were raised to \$10.00.

A special meeting of the House of Delegates was held last October at the Snow Shoe Club in Concord to consider the hometown care of veterans with service-connected disabilities. This meeting was attended by a representative of the Veterans Administration from Boston. Dr. Cooper as well as by Dr. Drury, of the Manchester office. The decision was left in the hands of a special committee, with power to act. This special committee had several meetings, drew up an agreement and prepared a fee table for the care of veterans. The agreement has been accepted by the Veterans Administration. The fee table was rejected in part, by the Administration on the ground that some of the fees were larger than those charged other patients for similar services in New Hampshire communities. The Veterans' Administration countered with a fee table that represented the maximum amounts that the Government was willing to pay. Copies of this fee table and of the agreement were sent to each county society with the request that it consider the matter and instruct its delegates in the proper action to be taken at this meeting.

The Taft Bill (S. 345) will probably have hearings in the Senate soon, and according to the newspapers a revised version of the Wagner-Murray-Dingell Bill is also to be presented.

The most important legislation that came before the General Court this year was the hearing on the elimination of Bangs disease in cattle. The Society was represented by the Committee on Public Relations. Dr. Blood spoke in favor of a continuation of the program and the Secretary gave a vivid description of undulant fever with which he was afflicted in 1941.

Our attorney Mr. Sulloway was given his usual retaining fee of \$100. It should be remembered that any member

of the Society is privileged to confer, without expense with Mr. Sulloway on any legal difficulty pertaining to the practice of medicine.

According to the by laws of the American Medical Association the delegate from this state, as well as the alternate delegate should be elected for two years rather than for one year. It should also be noted that both the delegate and the alternate delegate must have been fellows of the American Medical Association for a period of two years before they are elected.

A return postal card was sent to all members during the course of the year asking them to signify if they would like to serve on one of the committees of the Society. The names of those who wish to serve on a committee have been given to the Committee on Nominations.

A second postal card was sent soliciting volunteers for a speakers' bureau. A questionnaire was sent to all members requesting suggestions to make the work of the Society more interesting and more beneficial.

The Missouri State Medical Association sponsored a contest last year among school children who were asked to write a brief essay on the subject, "What Can Our Community Do to Improve Its Health?" Suitable prizes were awarded. It might be worth while to have such a contest in New Hampshire next fall. We might find some "sore spots" that could be corrected in a constructive way. If such a contest meets with your approval, I suggest the expenditure of \$200 to \$300 in prizes.

For the present, it seems that we must hold our annual meeting at some summer hotel in June. Now that we have returned to a two-day meeting it may be considered unwise to hold a meeting in Manchester because it is practically impossible in that city to get adequate hotel accommodations.

On motion duly made and seconded, it was voted that the report of the Secretary-Treasurer be referred to the Committee on Officers' Reports.

Dr. Macmillan, chairman of the Committee on Officers' Reports, then stated that the Committee had approved the Secretary's report.

The speaker then suggested that Dr. Metcalf say a little more regarding the question of sponsoring a contest among school children on community health.

Dr. Metcalf replied that the contest in Missouri apparently received a considerable response from the school children, that it gave the children and the people of Missouri the idea that physicians were trying to do something constructive for the betterment of health in the different communities and that, in the event that they picked up what he called a "sore spot," an attempt was made to correct that condition. The question was whether it would be worth while to try it in New Hampshire this fall.

Dr. Macmillan stated that the Committee on Officers' Reports had read Dr. Metcalf's report and approved all his suggestions.

Dr. Dye inquired whether funds were available for such a purpose.

The Secretary replied in the affirmative.

Dr. Dye moved that the Society sponsor such a contest, instructing Dr. Metcalf to proceed with it, and that the maximum expenditure be \$300.

This motion was duly seconded and carried.

Dr. Dye moved that the appropriation of \$100 for the expenses of the New England Medical Council be made.

The speaker asked if all the members knew what the New England Council was. He defined it as an organization of delegates from the six New England state societies to discuss the questions that concern the general region of New England. He said that it had no particular power of action but had power of recommendation to the societies, adding that it had conducted general discussions for the memberships of the societies, besides its own discussions, concerning the state of medicine in the New England area.

The President stated that he had attended all the meetings of the Council, which had been important in bringing the viewpoints of the different New England states together. He believed that the medical societies of the six New England states are today much more in accord than they have ever been before, because of the Council.

The Speaker then requested all those in favor of appropriating \$100 for the expenses of the New England Medical Council to manifest assent by saying "aye."

There was a chorus of "ayes," and the motion was carried.

The report of the Committee on the Control of Cancer was then presented by the chairman, Dr. George C. Wilkins.

As usual during the past year your committee sent to every member of the society three one-page letters on important subjects pertaining to cancer diagnosis or treatment. One on cancer of the urinary tract mentioned the two most important symptoms, hematuria and a mass in the flank. Any patient presenting either of these symptoms should be cystoscoped without delay, that an early diagnosis may be made. Cancer of the digestive tract was too large a subject to be treated in one letter, but several important points were emphasized that should lead to earlier diagnosis, such as early x-ray examinations in patients with indefinite but persistent digestive disturbances and repeat x-ray examinations when the diagnosis has been indefinite. Every tumor of the digestive tract should be considered a carcinoma until proved otherwise. More careful histories and more thorough examinations will reveal carcinoma of the colon earlier. This type of carcinoma is appearing more frequently in our cancer clinics and hospitals. Our last letter contained many unrelated hints in short sentences that might refresh the memories of physicians in the methods of making correct diagnoses of cancer and in advising adequate treatment.

The New Hampshire Medical Society was the first to send cancer information of this type to its members. Now many states are doing it, some by means of comparatively voluminous pamphlets and bulletins, but your committee still prefers short, readable articles, which we hope will stimulate interest. Complete information on any phase of cancer is available in medical magazines and in books.

On May 6 the second annual Cancer Instruction Day was held in Manchester. There were eleven speakers on different phases of cancer. All talks were short and concise. A luncheon was served at noon, and the members of the Society attending the meeting are indebted to the New Hampshire Field Army of the American Cancer Society for bearing all the expenses of the meeting as part of their educational campaign. Although ninety members had indicated their intention of attending this meeting, we were again disappointed at the small number of general practitioners attending.

The Field Army has also continued its generous offer of financial assistance to any physician connected with any of the state cancer clinics to take refresher courses at a cancer

center. Two physicians have taken advantage of this offer during the past year.

The lay and high-school educational projects of the Field Army have been continuously functioning, but there are still high schools that have not accepted the ideas or the pamphlets furnished by the Field Army.

The functions of the fourteen cancer clinics of the New Hampshire Cancer Commission have continued as usual. During the year ending July 1, 1946, the smallest number of new cases for several years was recorded. The number always fluctuates with economic conditions, and during the past six months more patients have appeared at the clinics and there have been more applications for financial assistance. Since 1931, when the Commission was established, these changes have been an early and significant barometer of economic changes.

The need for continued intensive education among the laity in the early signs of cancer is being constantly demonstrated by the appearance of patients with advanced cancer in doctor's offices, hospitals and clinics. We must also recognize and admit that there is a continued need for education in early recognition of cancer among the members of the medical profession. This is our problem, and we should do all in our power to remedy this situation.

Your committee expended \$55.56 of the \$60.00 appropriation and requests the sum of \$60.00 for next year's expenses.

GEO. C. WILKINS, Chairman

RALPH E. MILLER

WALTER H. LACEY

ALBERT OPPENHEIMER

GEORGE F. DWINELL

Dr. Macmillan stated that the Committee on Officers' Reports had approved the report of the Committee on the Control of Cancer.

Dr. Dye moved that the sum of \$60.00 be appropriated for expenses of the Committee on Control of Cancer. This motion was duly seconded and carried.

The report of the Council of the New England Medical Societies was then presented by Dr. Ralph W. Tuttle.

The Council of the New England State Medical Societies has had four meetings within the past year. The first meeting was held in Concord at the Snow Shoe Club on June 9, 1946. Aside from the delegates of the different State Societies there were the following guests: Dr. Robert O. Blood, Mr. James M. Langley, Mr. Frank J. Sulloway, Mr. George M. Putnam, Mr. Charles Gannon, Mr. Arthur J. Connors, of the American Federation of Labor, and Mr. Newell, member of the staff of the Concord Monitor.

Dr. Blood, chairman of the Committee on Maternal and Infant Care, gave an interesting account of the work of the committee in its educational program aimed at the reduction of maternal and infant deaths in the State.

Mr. James M. Langley, chairman of the State Hospital Study Commission, discussed the Hill-Burton Act.

Mr. Frank J. Sulloway, attorney for the Society, discussed methods of handling malpractice suits. He stated that the Society carries on a program of education to teach its members how malpractice suits arise and that three fourths of such suits are due to remarks of medical colleagues who do not know the full facts of the medical case. This education has been effective, as shown by the fact that the members of the Society have had the benefit of five successive reductions in the basic premium rate.

Mr. George Putnam, president of the Farm Bureau of New Hampshire and director of the National Farm Bureau, gave an interesting talk on the medical needs of the rural communities.

A representative of the American Federation of Labor was present at the meeting but did not address the group.

The topics for discussion at the next Council meeting were distributed as follows: public relations (Massachusetts), rural medical care (Vermont and Maine), prepaid insurance (Rhode Island), veterans (Connecticut), medical care (Rhode Island) and licensure (New Hampshire).

The next meeting of the Council was held in Boston at which the subjects stated were taken up. The secretary of the Council Mr Farrell mailed the minutes of the previous meeting to all the members and also had the proceedings mailed and the report on Rural Health Care published in the *Rhode Island Medical Journal*. He sent to each member of the Council reports on the progress of the bills relating to medicine in the United States Senate and House of Representatives.

Dr Tighe, representative from Massachusetts reported on the question of medical public relations. He stated that the Council of the Massachusetts Medical Society had created a new position, Director of Medical Information and Education and that this officer will be charged with organizing two divergent programs a medical education program and one designed to place that society in a more favorable light before the public. Several of the state medical societies have a full time officer to publicize their activities. In some states he is a doctor and in others a layman. It was stressed that public relations is an important part of our endeavor if we wish to maintain the practice of medicine throughout the country in its present form and keep out from under complete governmental control.

Dr Metcalf reported on the seventh annual Congress on Industrial Health sponsored by the American Medical Association, this being the first time the congress has been held outside Chicago. Full co-operation was given by the Council to the American Medical Association and the Massachusetts Medical Society, which sponsored the meeting. The report of the scientific papers presented at the Congress has been published in the *Journal of the American Medical Association*. Programs distributed by the American Medical Association nationally carried us as cosponsor of the Congress.

After a discussion of the Kenny Foundation Campaign, Dr Creighton Barker of Connecticut moved that it be the opinion of the Council of the New England State Medical Societies that the societies in this area should withhold approval of the Sister Kenny Foundation Public Appeal for funds in the opinion that it should secure its funds from already existing organizations to avoid duplication in programs for the control of poliomyelitis. This motion was accepted and unanimously adopted.

Dr Pitts, president of the Rhode Island Medical Society spoke on prepaid insurance and medical-care plans, which were discussed by the delegates from the several states.

Dr Metcalf reported for the New Hampshire Society that the Blue Cross had 173 000 subscribers the Blue Shield Surgical 68 000 and the Blue Shield Medical 15 000. At present the enrollment is much larger. The members from the other states were quite interested in this report. Maine has not done so well as some of the other states because there is more or less difficulty with the osteopaths. Maine is thinking of endowing a private insurance carrier to write its medical insurance rather than the Blue Cross. The decision has not yet been made. Vermont has adopted the plan of the New Hampshire Physician Service and has formed an alliance with New Hampshire. Connecticut is still working out a program of its own which will probably be somewhat similar to ours.

Dr Cole Gibson, president of the Connecticut Medical Society, reported on the National Physicians Committee meeting in St. Louis. He discussed the work of the committee in Washington and called attention to the recent splendid publication put out by the committee under the title *The Key to Collectionism*.

Dr Miller of Connecticut, inquired if any of the men present had any pronounced opinion concerning the situation whereby trustees of the American Medical Association have also served on the Board of Directors of the National Physicians Committee. There was rather a brief discussion of this point, and Dr Metcalf called for a show of hands as to whether it was believed that there should be separation as regards such participation. The vote showed that nine signified that they believed the trustees of the American Medical Association should not also serve on the Board of Directors of the National Physicians Committee. There were no negative votes, but several members did not vote on the question.

The agenda for the next meeting included hospitals (New Hampshire), group practice (Connecticut), health education (Rhode Island), labor relations (Massachusetts), legislation (Vermont) and medical economics (Maine).

The third meeting of the Council was held in Boston in January. As usual there was an excellent attendance. Guests at this meeting were Dr. Frank J. Lawless, Harold Q. Gallupe, John A. Bolster and John S. Wheeler, respective secretaries of the boards of registration in medicine in Vermont, Massachusetts, Rhode Island and New Hampshire and Dr. Leroy E. Parkins, chairman of 1946 Postgraduate Assembly, and Mr. Robert St. B. Boyd executive secretary of the Massachusetts Medical Society.

There was a proposal from the Massachusetts Medical Society that the New England Postgraduate Assembly, hitherto sponsored by the Massachusetts Medical Society with the co-operation of the other New England medical societies be sponsored by the New England societies through the Council of the New England State Medical Societies. After considerable discussion it was decided that the Council was not in a position to commit the different state societies to the sponsorship of the program without having approval from the respective societies. This is a problem that should be taken up by each of the medical societies for a report to the Council next year. The Massachusetts Medical Society will sponsor the New England Postgraduate Assembly this year as they have previously done, waiting confirmation by the different state medical societies as to whether they wish to co-operate with the Massachusetts Medical Society in sponsoring meetings in 1948.

Prior to the war the Assembly was held at Sanders Theater in Cambridge. No exhibits were permitted, but a nominal registration charge was made of persons attending the Assembly. The registration in 1941 was 699, and the total income was \$2,828.25. A net profit of \$301.41 was realized.

In 1946 the Assembly was renewed and was held at the Hotel Bradford, Boston. Exhibits were permitted. The total registration of physicians was 488. The income from exhibits was \$3 600, and from registrations and tickets, \$3 202.45. The total income was \$6 802.45 and the total expense was \$5 964.97. The net profit of \$837.48 accrued to the Massachusetts Medical Society.

It is planned to hold the 1947 Assembly at the Copley Plaza Hotel, Boston, on October 29, 30 and 31. The ballroom, foyer, Colonial Room and Sheraton Room are to be used for exhibits and meetings. Possible income from exhibits is expected to be \$4 500. (Forty five registrations at \$100 each.) Hotel rental charges are expected to be \$1,115. Luncheons for two days and dinner for one evening will be at the regular charge to registrants. The registration fee for 1947 will be \$2.00.

The question arises, Does the New Hampshire Medical Society wish to sponsor the Assembly?

Dr Metcalf reporting for the subcommittee of the Council representing the New Hampshire delegation on the subject of hospitals in the post war world read the following summary of a complete report submitted by the committee.

We suggest the following trend in hospitalization in the post war world:

Expansion of the general hospital with increasing acceptance of communicable diseases of certain types of tuberculosis of nervous and mental ailments and perhaps in separate pavilions, of care for patients in the convalescent and chronic stages.

Increasing subsidies from the federal, state or county governments. The Hill-Burton Bill provides a subsidy. For "relief" patients the Government under its different programs pays only about 50 per cent of the actual cost of medical care. It should pay the entire cost for the patient so classified.

Extension of physical and occupational therapy. State licensure for all institutions that care for the sick—supervised we hope by one agency.

Responsible boards of trustees who will co-operate with the medical staff and with a sure fire administrator who has his feet on the ground.

Two groups of nurses, besides the graduates—the first group with better background and a longer train-

ing period, and the other, for the simpler tasks, with briefer training

Higher wages for nurses and for all hospital personnel The American Hospital Association is working on the problem of pensions Social Security does its part, but it should be furthered by a fund contributed by the hospital and the employees themselves

An increase in the number of doctors who have their offices in hospitals and an increase in group practice.

A gradual increase in the cost of hospital care, which will be materially alleviated by insurance plans

Public-health centers in areas of scanty population, rather than an increase of small hospitals

Closer co-ordination among hospitals, perhaps under the sponsorship of hospital councils

In discussion Dr Pitts reported that he had been informed that there had been no applicants for the new nursing class at Rhode Island Hospital that was to start in February, showing that the nursing situation promised to become critical

Dr Rice, of Massachusetts, discussed the program in that state for licensed attendants Dr Gallupe, secretary of the Massachusetts Board of Registration, stated that the board had approved eleven schools for licensed attendants with courses running from one year to eighteen months He expressed the opinion that it was an excellent method to provide nurse auxiliaries He further reported that Boston University was planning to inaugurate a five-year course in its new school program Dr Yeager, of Connecticut, stated that at a recent nurses' meeting in Hartford there had been much discussion of why nurses do not start training because of the conflict between nurses with college education and those with high-school training He also reported that industry had attracted many nurses and nursing personnel

Dr Tighe, of Massachusetts, spoke on labor relations He cited the two questions proposed the advisability of meeting with labor leaders and the discussion of mutual problems regarding health and welfare He recommended that for the time being action on a meeting be postponed He amplified his reason with remarks off the record He observed that it was the general belief of labor that industry should pay the costs of medical care, whereas industry considers the main expense involved in assisting in medical care for employees, other than inpatient plant service, to accept the cost of services involved for payroll deductions and so forth, to enable employees to purchase insurance, both from nonprofit and from casualty carriers Dr Welch remarked that one source of opposition from employers has been the fact that wage increases are known and publicized but that insurance benefits are not given equal publicity, hence, employers are not too favorably inclined to expand or to continue some of their programs now in operation

Dr Pitts spoke on health education He reported that the subcommittee assigned to the topic had decided to concentrate on the matter of statewide health federations or councils under the sponsorship of the medical societies Men from each state reported that there was some health-education plan in each of the different states They believed that this subject should be taken up more fully by the state medical societies

The subject of medical licensure was brought up The secretaries of the boards of registration in medicine in Vermont, Massachusetts, Rhode Island and New Hampshire were present, following a meeting of their own in another room The following report was submitted at this meeting, and as a result of the adoption of these regulations, licensure by endorsement will be possible in all the New England states except Maine, where the statutes prohibit it

The Rhode Island licensing authorities have given careful consideration to the possibility of establishing reciprocal relations with other New England states for the issuance of medical licenses The Rhode Island Medical Board does not consider straight reciprocity advisable or permissible under the present medical act. The board has voted, however, to exempt any licensee from another New England state from the usual written

examination, provided the requirements of the Rhode Island law are fully met by the individual applicant. Such candidates will be treated in the same manner as diplomates of the National Board of Medical Examiners After evaluation of their credentials, they will be required only to appear before the Board of Examiners for an oral examination, which is actually more of an interview than an examination

It should be emphasized that the issuance of medical licenses by endorsement after oral examination is discretionary with the board A licentiate who is not in good standing with the licensing authorities of his home state will, of course, not be considered Also, Rhode Island will consider candidates for endorsement from only states that extend the same privilege to physicians registered in Rhode Island

Recently, the Rhode Island Board of Examiners in Medicine held a joint meeting with the Board Examiners in the Basic Sciences, and the latter will issue a certificate of ability in the basic sciences by endorsement after oral examination to candidates who meet the following qualifications

That he has passed in another state an examination in the basic sciences held before a board of examiners in the basic sciences or before a state board authorized to issue licenses to practice the healing art.

That the requirements of that state are not less than those of Rhode Island so far as the basic-science subjects are concerned

That the board of examiners in the basic sciences of such state grant like exemption to persons holding Rhode Island certificates in the basic sciences

The fee for a certificate by endorsement would be the same as that for the regular examination — \$10.00 in the basic sciences and \$20.00 in medicine

The fourth meeting of the Council was held at the Harvard Club of Boston on April 16, 1947, with the usual full attendance Mr John E Farrell, the executive secretary, gave an excellent report of the activities of the year

Dr Metcalf called for discussion on the proposal of the executive secretary in his annual report for regional conferences of committees of the various state medical societies in this area on various problems concerned with medical economics Dr Miller, of Connecticut, suggested that copies of this report be submitted to Dr Lull, secretary of the American Medical Association, with a request that he in turn submit it to the committee planning the Conference for County Medical Society Officers at the time of the American Medical Association meeting in June He expressed the opinion that the idea of regional meetings should be incorporated in the discussion at this particular conference He also stated that it might be advisable to have the various state societies in New England know of the desire of the Council of the New England State Medical Societies to assist them in educating their various committees in mutual problems regarding medical economics This was discussed favorably by several members of the Council

Dr Metcalf summarized the opinion that the executive secretary should notify the secretary of each medical society regarding the desire of the Council to sponsor such conferences, and also to inquire whether the respective committees in the societies wished to participate at a meeting in the fall, possibly on the subject of medical public relations

The executive secretary, in the absence of Dr Rice, read his report regarding financing the Council, as follows

At present there seem to be two ways of raising funds for this Council The first is in the way it has been done by assessing each state society the same amount Naturally, state societies with small memberships believe that they should not pay so much as state societies with larger enrollments The second way would be to assess each state society an amount proportional to its membership roll Again, quite naturally, state societies with large enrollments believe that they are carrying too much of the financial load This method was tried a generation ago by an organization similar to this and came to grief over the issue

There might be a third way. The Council hopes to take over the Postgraduate Assembly, conducted for several years by the Massachusetts Medical Society. Is there not reason to believe that this venture could be so managed as to yield enough profit to enable the Council to undertake further activities?

If this offer seems unwise, the conclusion is that this Council should raise its funds, as heretofore, by equal assessments from each state society.

Drs. Howard, O'Hara and Gibson entered the discussion and expressed the opinion that the Council should not branch out at this time. Therefore Dr Metcalf moved that the Council continue to finance its program as in the past with each of the state medical societies contributing \$100. Dr Cole Gibson seconded the motion, which was unanimously adopted. It will be necessary for the House of Delegates to appropriate \$100 for this purpose.

The president stated that a request would be sent to the Secretary of each of the medical societies requesting that official delegates be named at the time of the annual meetings of the various societies. Mr Farrell called attention to the fact that it has been the policy to invite past delegates to attend all Council meetings and he suggested that some official action should be taken in this matter.

Dr Gibson moved that all former members of the Council of the New England Medical Societies be officially designated as honorary members and that they be invited to attend the meetings of the Council and, further, that from time to time such honorary members be communicated with to see if they wish to continue on the mailing list of the Council to receive notices and invitations of meetings. The motion was seconded and unanimously adopted.

The nominating committee submitted the following nominations for officers for the ensuing year: for president, Dr Arthur H. Ruggles, Rhode Island; for vice president, Dr Stephen A. Cobb of Maine and executive secretary, Mr John E. Farrell, of Rhode Island. Dr Pitts moved that the nominations for officers be closed; the motion was seconded and approved. He then moved that the secretary be empowered to cast one vote for the slate as nominated. The motion was seconded and unanimously adopted.

Dr Norman H. Gardner, of Connecticut, a member of the National Committee on Rural Medical Service of the American Medical Association, addressed the Council on the matter of planning for rural medical services by state medical societies. There was a general discussion of the subject. Dr Gardner reported that the Connecticut State Medical Society planned to conduct a conference on rural health at Connecticut University at Storrs on July 16, and he requested that the Committee on Rural Health in each state society attend this conference. Mr Ambrose B. Kelley, a former member of the Committee on Social Insurance of the National Association of Mutual Casualty Companies and a guest of the Council, commented on the procedure regarding the writing of insurance by private companies for persons living in rural areas, and stated that the private insurance companies cannot write the contracts on an individual basis at a low cost. He observed that the Grange in many communities works closely with the Farm Bureau and has served as an excellent outlet for the distribution of insurance. Dr Metcalf reported in detail on the situation in New Hampshire, and Dr Gardner closed the discussion by urging that each state have a rural-health committee to strengthen the work of the national committee so that it will be in a position to report that there was an active committee in every state concerned with the problem.

Dr Reginald F. DeWitt, of Plymouth New Hampshire spoke on the subject of group practice in a small community. An interesting discussion followed.

Mr Kelley spoke on the relation between the medical profession and the insurance companies and the problem of socialized medicine. In discussing national legislation he pointed out that the proponents of the Wagner-Murray-Dingell Bill had proved themselves better salesmen than the physicians whose case may have been better and whose logic was probably irrefutable but whose dramatization of the problem fell far short of that of the social plan-

ners who appealed to the emotional phases of the entire issue.

Dr Macmillan then stated that the Committee on Officers' Reports approved the report of the Committee to the Council of the New England Medical Societies and suggested that it be accepted.

The President observed that if the House of Delegates wished to approve the recommendation that the Council of the New England State Medical Societies sponsor the Postgraduate Assembly, it could report to the Council that it had done so but that each of the other states would have to act similarly before the Council could sponsor the assembly. He added that sponsorship would not entail any expense on the Society, unless for some reason the assembly which had heretofore been profitable, should fall far short. The Assembly would be better attended, if each state had its own sponsorship, instead of sole sponsorship by the Massachusetts Medical Society, and this course would probably make the Assembly much larger than it is at the present time.

Dr Sullivan stated that sponsorship of the assembly by the New England Council would involve six hundred members and, if it were a success, even more. He asked for suggestions concerning where meetings could be held.

The Speaker observed that the assembly need not be held in New Hampshire and that some central city, such as Boston or Worcester, would be better able to accommodate the members.

A member inquired if the profits, if any, would accrue to the Council or to the Massachusetts Medical Society.

The President replied that profits would definitely accrue to the Council and that if the profits were large enough, the \$100 supplied every year would no longer be necessary. He added that if the Council could become a concrete entity, which, in itself, might have a backlog after a few years, it could expand and do far more toward the promulgation of the good of the practice of medicine in all New England. He moved that the House of Delegates be empowered to vote in favor of the sponsorship of the new assembly. This motion was duly seconded.

The Secretary stated that the Assembly had always been held in Boston, with usually three or four hundred physicians from Massachusetts and a scattering from the other states. Last year, he added, there were 23 men from New Hampshire. He therefore believed that there would probably be a large attendance from Massachusetts, Connecticut and Rhode Island and that the meetings should be held in Massachusetts, perhaps in Boston. Consequently, the Massachusetts Medical Society would have to continue active support.

He then raised the question what would happen under the proposed sponsorship, if there was a deficit in any year. The assumption was, on the part



of the men from Massachusetts, that that deficit would be taken from the several New England medical societies, pro rata. In other words, the Massachusetts Medical Society would pay a larger proportion of the deficit than the New Hampshire Medical Society.

He assumed that the Massachusetts Medical Society would ordinarily run the meetings and that there would be a delegation from New Hampshire, which would be on the executive or sponsoring committee and would try to interest the men in New Hampshire in this meeting.

The Speaker then requested all those in favor of the motion to manifest assent by saying "Aye."

There was a chorus of "ayes," and the motion was carried.

The report of the Committee on Maternity and Infancy was then read, as follows:

This is the thirteenth year in which the New Hampshire Medical Society, through the Committee on Maternity and Infancy, has conducted a study of maternal and infant deaths during the previous calendar year. The study is conducted with the co-operation of the New Hampshire Department of Health, which gives the services of personnel in the divisions of Maternal and Child Health and Vital Statistics. All data are gathered by the Division of Maternal and Child Health, acting as agent for the Committee on Maternity and Infancy. Death reports are received in the Division of Vital Statistics and, after checking and coding of the causes recorded on the death certificates, are transmitted to the Division of Maternal and Child Health for follow-up information on each case. The members of the committee, it should be pointed out, do not know the identity of the patient, physician, hospital or community where the patient was delivered. It is important to point out that a study of this kind is made possible only through the co-operation of the reporting physicians, since decisions made are based entirely on the information at hand. The committee has endeavored, as in all past studies, to analyze openmindedly all information in each case that can be obtained and has attempted to appraise the data so far as possible, having the advantage of reviewing the events in retrospect and not admittedly being in the position of the physician in charge of the case, who must make his decisions on the spot. It is with this thought in mind that the committee wishes physicians to read the recommendations and suggestions made, with the hope that such comments as are made may be of value in the conduct of future cases presenting similar problems.

The committee wishes to emphasize the fact that this report and study are for the purpose of making available to the practicing physician information on maternal deaths and their causes. It is therefore essential that physicians respond as promptly as possible, giving as full information as they can on each case reported by them, this year, only two physicians failed to respond to the committee's request.

As a matter of record, the committee believes that the method of conducting this study should be described. After the data have been gathered, either through personal contact of a member of the Department of Health or by letter, the information is presented to the committee without identifying information. Each member of the committee has a copy of the report to study. A discussion of the details concerned with each case ensues. Then the decision of the committee is recorded. The committee classifies the causes of death in accordance with the facts. This classification may differ from that of the Division of Vital Statistics, according to the *International List of Causes of Death*. The only information that the Division has, of course, is the diagnosis of the physician recorded on the death certificate. The discrepancies in classification, therefore, are based on the fact that as the com-

mittee receives additional information the cause of death becomes more apparent. This year, for instance, there were 4 deaths reported as maternal deaths that the committee considered to be due to other causes, such as surgical shock and, in 2 cases, anesthesia. One death was believed to be due to self-inflicted poison.

Over the years during which these studies have been performed, there has been a real decrease in the maternal death rate. The committee would like to suppose that its efforts in indicating poor obstetric procedures to individual physicians is—in part, at least—responsible.

TABLE 1 Number of Maternal Deaths by Cause

CAUSE	NO OF DEATHS	
	ASSIGNED BY INTERNATIONAL LIST OF CAUSES OF DEATH	ASSIGNED BY COMMITTEE
Abortion (spontaneous, therapeutic or of unspecified origin), with mention of other infection	1	
Ectopic gestation, with mention of infection	1	1
Other and unspecified hemorrhage of pregnancy	1	1
Other toxemias of pregnancy	1	1
Other and unspecified hemorrhages of childbirth and puerperium	2	2
General or local puerperal infection (except pycitis)	1	1
Puerperal thrombophlebitis	1	
Puerperal embolism and sudden death	1	1
Puerperal eclampsia	2	2
Other puerperal toxemias	3	2
Other specified conditions of childbirth	1	2
Other and unspecified conditions of childbirth and puerperium	1	1
Unknown	—	2
Totals..	16	16

for this fact. Tables 1-5 present the causes of death and other data on maternal deaths since 1933.

The committee further classifies the cases into four groups, as follows:

*Group I* Cases in which the patient was at fault because of refusal of prenatal care, neglect, self-induced abortion and so forth (1 case).

*Group II* Those in which the obstetric treatment was inadequate (2 cases).

*Group III* Those in which death was apparently unavoidable (7 cases).

*Group IV* Cases in which data were insufficient, and in which the cause of death was therefore undetermined (6 cases).

(It has been found that in some cases inadequate information frequently signified inadequate treatment.)

After the committee has made a decision in each case, including suggestions for conduct in the individual case,

TABLE 2 Maternal Deaths according to County

COUNTY	URBAN	RURAL	TOTAL
Belknap	0	0	0
Carroll	0	0	0
Cheshire	0	0	1
Cook	1	0	0
Grafton	0	0	8
Hillsboro	8	0	2
Merrimack	2	0	0
Rockingham	0	0	4
Strafford	4	0	1
Sullivan	1	—	—
Totals	16	0	16

a letter containing this information is written to the reporting physician. It is hoped that this procedure will aid physicians in selecting the proper treatment for their patients. The committee fully realizes how much easier

it is to decide the course of a case at a round table discussion than at the bedside at the moment when treatment is necessary.

In the study of maternal mortality by years it is interesting to note that the highest rate occurred in 1933, at about the time that the studies began. There has been a slowly receding rate through 1942, but in 1943 there was a rise in the rate, which remained stationary through 1944 and started to drop again in 1945. The rate in 1945 was 18 per thousand live births. The number of maternal deaths was 16 with a slight decrease in the number of births as compared with the previous year. There were 8551 births in 1945. In 1946 the year of this study, 16 maternal deaths were reported and the birth rate reached an all-time high. The number of births reported was 11,489. This gives a maternal death rate of 1.4.

The committee is not discussing infant deaths or stillbirths in this report but Table 3 presents the causes of death among infants under one year of age and Table 4 a list of the chief causes of death in stillbirths. The committee would like to call attention to the number of infant deaths. It is believed that the accepted definition for a stillbirth should be restated in this report: the statistical definition adopted for use in the United States and the one accepted by the Children's Bureau of the American Public Health Association, the Bureau of the Census and the one now in use in New Hampshire is as follows: "A fetus showing no evidence of life after complete birth (no action of heart, breathing or movement of voluntary muscle) if the twentieth week of gestation has been reached should be registered as a stillbirth."

#### MATERNAL DEATHS

During 1946 a total of 16 maternal deaths were reported. The number of births in the state was 11,489 giving the official rate on the basis of 16 deaths in terms of 1000 live births of 1.4. It is gratifying to the committee that in the majority of the deaths were unavoidable because of insufficient data, however or no data at all the committee has had to classify more maternal deaths as "undetermined" than in any previous years.

In the group of deaths for which responsibility was undetermined, it was interesting that there were 2 cases of inversion of the uterus. From what could be ascertained both patients died of post partum hemorrhage after the uterus had become inverted during the third stage of labor. This condition is admittedly a startling and sometimes dramatic situation. The committee wishes to suggest that no placenta should ever be delivered by a Credé maneuver unless one hand is between the fundus and the symphysis. If this procedure is observed inversion of the uterus cannot occur. (By a Credé procedure is meant the squeezing of the uterus by the exertion of anteroposterior pressure and avoidance of downward pressure. Delivery of the placenta should not be attempted until it is obviously detached.) It is recognized by the committee that spontaneous inversions occur but also that every attempt should be made to avoid such a situation by warning against a forceful Credé and taking the precaution described above. In 1 case the committee believed that, although the physician described replacing the uterus, despite which bleeding persisted the uterus may have been pushed back into the vagina without completely reducing the inversion.

The causes of other undetermined deaths were given as follows: chronic nephritis with premature delivery of six month, stillborn twins and uremia with a stillbirth after which multiple infarctions were found in the liver and kidney with a complicating thrombophlebitis.

The group that the committee classified as unavoidable posed some interesting problems. These cases fell into two groups: death occurring from intrauterine or post-partum hemorrhage and toxemia of pregnancy. One of these cases was a woman of twenty-eight years of age who, during her fourth pregnancy developed a sudden attack of acute lower abdominal pain that came and went at varying intervals. Examination during these attacks revealed nothing unusual and although she had been admitted to a hospital for study she was discharged twice with no findings. There was no external bleeding and finally the patient in her last attack went into shock and expired. Autopsy revealed torsion of a five month pregnant uterus filled with blood. The interesting fact

in this case was that there was a history of a ventral fixation of the uterus several years previously the patient, however had gone through a normal pregnancy and delivery following that operation and it is difficult to explain why torsion did not occur at that time but was the final cause of death in the later pregnancy. The committee believes that a ventral fixation, similar to the so-called "Kelley ventral fixation," should not be performed in the child-bearing age.

Again, in 1946, the leading cause of death in the cases studied was toxemia of pregnancy. In several cases it was noted that the treatment given to eclamptic patients

TABLE 3 Infant Deaths under One Year of Age from All Causes

CAUSE	MALE INFANTS	FEMALE INFANTS	TOTAL
Whooping cough	3	4	7
Septicemia and purulent infection (non puerperal)	1	0	1
Influenza without respiratory complications specified	1	1	2
Measles	1	0	1
Cancer of other and unspecified organs	0	1	1
Hemophilia	0	1	1
Meningitis (not due to meningococcus)	0	1	1
Convulsions (patient under five years of age)	1	0	1
Diseases of lymphatic system	0	1	1
Bronchitis acute	0	1	1
Bronchitis, unspecified	1	0	1
Bronchopneumonia (including capillary bronchitis)	11	9	20
Lobar pneumonia	1	4	5
Facemollia (unspecified)	4	3	7
Ulcer of stomach	1	0	1
Diarrhea and enteritis	14	10	24
Intestinal obstruction	1	0	1
Cirrhosis of liver without mention of alcoholism	0	1	1
Peritonitis (cause not stated)	2	0	2
Acute nephritis	1	0	1
Congenital hydrocephalus	3	8	13
Epina bilis and megalocoele	2	2	4
Asenkephalia	2	2	4
Congenital malformations of heart	18	8	26
Congenital malformations of digestive system	2	-	2
Congenital malformations of genito-urinary system	1	0	1
Other and unspecified congenital malformations	1	1	2
Congenital debility (cause not stated)	3	1	4
Premature birth (cause not stated)	64	40	104
Intrauterine or spinal hemorrhage	14	10	24
Other injuries at birth	7	2	9
Asphyxia (cause not specified) atelectasis	9	4	13
Other specified diseases peculiar to first year of life	10	1	11
Accidental mechanical suffocation	4	4	8
Accidental injury by fall	1	0	1
Obstruction, suffocation or puncture by ingested objects	0	1	1
Other and unspecified accidents	1	0	1
Sudden death	1	0	1
Ill defined	1	1	2
Unknown or unspecified	1	-	1
<b>Totals</b>	<b>199</b>	<b>131</b>	<b>330</b>

was sodium chloride or mention of glucose and hypertonic salts was made. The committee wishes to stress the fact that eclamptic patients should not be given sodium chloride and that early treatment of toxemia is imperative. One case of toxemia was charged to the patient, who did not appear for prenatal care but presented herself in labor with a high blood pressure, a +++ test for albumin in the urine and definite signs of toxemia. Even though the physician instituted immediate treatment with magnesium sulfate and hypertonic glucose and delivery was spontaneous the patient died fourteen hours later. The committee repeats its recommendation concerning the treatment of toxemia — namely that as soon as the condition has been discovered the patient be given magnesium sulfate that early induction of labor be performed in accordance with the degree of prematurity that glucose be given intravenously with magnesium sulfate in severe cases and that oxygen and digitalization be employed in convulsive toxemias. It was of interest that the cases of toxemia reported in this series showed evidence of definite chronic nephritis or previous kidney damage. The committee doubted whether 1 case so reported was a

true toxemia, since the blood pressure was low and the signs not too clear cut. The committee believes that if permission for autopsy could be obtained in more of these cases, a definite diagnosis could be made, the fact that more autopsies are not performed is deplored.

The most striking fact concerning the type of cases studied this year was the lack of puerperal infections. There was only 1 case in which the mention of an infection was made. In this difficult case a young primipara, who had had a perfectly normal prenatal course and who had received excellent prenatal care, had a short tempestuous labor of three and a quarter hours and delivered a stillborn child. It was believed that these events indicated a premature separation of the placenta. The course that followed was tragically futile in that, despite every effort on the part of the physician and the consultants, the patient continued to bleed profusely and developed a post-partum infection. Every treatment, including the use

TABLE 4 *Chief Causes of Stillbirth according to Sex*

CAUSE	MALE INFANTS	FEMALE INFANTS	TOTAL
Conditions in fetus, placenta and cord			
Congenital malformations (incom- patible with life)	13	31	44
Placental and cord condition	27	21	48
Birth injury (fetal death during labor)	7	3	10
Syphilis	0	1	1
Infection other than syphilis	0	0	0
Erythroblastosis foetalis	3	0	3
Other abnormality in the fetus	0	2	2
Conditions in mother associated with fetal deaths			
Syphilis	1	2	3
Tuberculosis	0	0	0
Diabetes mellitus	0	1	1
Chronic disease of circulatory system	0	0	0
Chronic disease of genitourinary system	3	0	3
Other chronic disease	1	0	1
Other acute disease and conditions	2	0	2
Hemorrhage without mention of placental conditions	0	1	1
Toxemia of pregnancy	9	10	19
Infection	0	0	0
Difficult labor	3	5	8
Other accidents and violence	1	1	2
Ill defined and unknown	65	47	112
Totals	135	125	260

of penicillin, was given, and heroic efforts were made to control the infection and the bleeding. It was known that there was a lower uterine-segment laceration, as well as infection, and as a last resort the physicians decided on a hysterectomy, taking the chance of a fatal infection but realizing that anything less would probably result in a fatal hemorrhage. The patient did remarkably well after operation, but, despite transfusions and intensive treatment for the infection, she could not handle the infection enough to prevent the sloughing of the cervix, with hemorrhage, that finally caused her death about three weeks after operation. This case, because of its severity and possibly because of an individual resistance to the use of modern weapons against infection, is the exception rather than the rule. With the use of penicillin and the sulfonamides, the number of deaths due to infection has definitely decreased.

Another group of cases that deserve comment are those due to anesthesia. The importance of anesthesia during labor and delivery is emphasized, it is essential that a qualified anesthetist administer the anesthetic. The committee believes that a spinal or caudal anesthetic, when chosen, should be given only by qualified physicians trained in such techniques.

The following opinion of the New England Society of Anesthesiology concerning the question of anesthesia may be of value to physicians in the consideration of the importance of anesthesia.

It is the opinion of the New England Society of Anesthesiology that the administration of anesthesia is a form of medical practice.

A thorough grounding in all stages of medicine is essential for the selection of the proper agent and method and for its safe administration.

There are so many dangers inherent in all types of anesthesia that the success and safety of all the various methods is directly proportional to the experience and training of the person responsible. These dangers are so numerous and serious accidents are so imminent that it is imperative for a physician to be in constant attendance throughout the entire administration.

Serious or potentially fatal complications are especially prone to occur during the course of intravenous anesthesia, spinal anesthesia and caudal analgesia. Since these accidents are usually preventable it is our opinion that a physician conversant with these dangers should be in constant attendance.

#### COMMENTS AND RECOMMENDATIONS

The committee wishes to state that adequate study and recommendations are possible only if the physicians in New Hampshire co-operate in the task of promptly presenting full data. This year, the study was made exceedingly difficult because of lack of response to the requests concerning the cases of maternal deaths reported. The data were either incomplete or lacking. Two physicians failed to respond at all. On the other hand, the majority of physicians who returned information did so completely and promptly.

It is recommended that intensive efforts to obtain permission for autopsy be made on the part of physicians after maternal deaths. This will usually assure a more accurate diagnosis and will thus avoid some of the discrepancies that occur in the final reporting of maternal deaths. It should eliminate to a large degree the element of guesswork in the final analysis.

The committee wishes to stress the importance of good prenatal care when patients present themselves early in pregnancy. It was noted that in some cases in which the patients were seen by the third month, physicians failed to do regular prenatal examinations. In at least 1 case of toxemia, the patient was allowed to go into convulsions without the institution of treatment. It is well recognized that many patients are careless about reporting to the physician early in pregnancy or are reluctant to admit their situation and to seek medical care. The committee wishes to recommend further that, when a physician is fortunate enough to have a patient seek his advice, he render the best possible prenatal care. The most important initial part of this care should consist of a complete physical examination, including laboratory tests, and a complete history, so that a thorough appraisal of the patient's past, present and future status can be determined.

The committee wishes to reiterate its recommendation that eclamptic patients be treated by the use of magnesium sulfate in the early stages, early induction with careful planning as to the stage of pregnancy, glucose and magnesium sulfate in severe cases and the use of oxygen and digitalization in convulsive toxemias. The administration of sodium chloride should never be condoned, and the drug should definitely be excluded from the therapy of toxemic patients.

The committee wishes to repeat its opinion concerning the importance of trained anesthetists. The training of physicians in the skill of anesthesia should be encouraged.

The committee wishes to comment on the apparent drop in the number of post-partum infections as a cause of death. It is hoped that with the continued use of penicillin and other modern weapons against infection this cause of death in maternity cases will be eliminated. It is recognized that individual cases present impossible problems owing to individual resistance or drug idiosyncrasies.

The committee wishes to encourage better record keeping on the part of physicians and hospitals. After a lapse of time, the type of record that is carried around in the head becomes of no value and cannot be used as a defense or safeguard for any purpose. Good records are a good investment for both the hospital and the physician.

The committee wishes to thank the physicians and hospitals that responded to their requests for information concerning maternal deaths and for the help they rendered in making this report possible. The committee will be happy to receive any recommendations or suggestions from the physicians throughout the state that may be helpful regarding these annual reports.

The committee wishes to acknowledge with appreciation the co-operation of the State Department of Health, through its divisions of Maternal and Child Health and

TABLE 5 *Maternal Death Rates by Year (1933-1946)*

YEAR	RATE %
1933	6.3
1934	5.4
1935	6.1
1936	4.8
1937	4.3
1938	3.8
1939	3.1
1940	3.1
1941	1.9
1942	1.7
1943	2.7
1944	2.9
1945	1.8
1946	1.4

Vital Statistics, in furnishing data and personnel in the preparation of this report.

ROBERT O BLOOD *Chairman*  
BENJAMIN P BURPEE  
JAMES SANDERS

Dr Macmillan moved the acceptance of this report

This motion was duly seconded and was carried  
Dr Dube then presented the report of the Committee on Medical Economics, as follows

#### *New Hampshire Physician Service*

The past year has been one of rapid expansion and development. The most important step taken has been the extension of the service to Vermont, with the transformation of the Corporation to the New Hampshire-Vermont Physician Service, effective last October. The membership of the Corporation and the Board of Directors and its subcommittees has been expanded to include representation from Vermont. The Vermont Medical Society has been active in enrolling its members, and an enthusiastic response has been made.

Since the program in Vermont is still in its initial stages the figures given below refer almost exclusively to the New Hampshire Physician Service.

Growth in enrollment has continued at a gratifying rate. Of the forty five medical service plans in the United States that are associated with Blue Cross and have a total enrollment of 4,200,000 our own service now stands fourth in size.

There are at present, in round numbers, 110,000 subscribers to the Surgical Division and of these 40,000 are also enrolled under the Medical Division. It is interesting that the latter group, which increased at a much slower rate than the surgical in the first two years, is now expanding at approximately the same rate as the surgical.

Favorable loss ratios in both divisions have made possible an increase in benefits. There has been an upward revision of many items in the surgical schedule, and allowances for medical visits have been increased. The first step in preventive medicine has been taken with provision under the medical contract for allowances for immunization injections for infants under one year of age.

#### *Veterans' Care*

A highly significant development in the field of medical economics is the inclusion of the private physician in the program of medical care for veterans. The contribution of medical-school faculties under supervision of the dean's committee has made possible the present high standard of service achieved in Veterans Administration hospitals. A further step in the program is the utilization of the local physician in providing care for service-connected disabilities of the veteran. This arrangement is in effect in several states and is being presented for the consideration of this session of the House of Delegates.

This program is, of course, a form of so-called "government medicine." It is set up, however in accordance with the principle previously advocated by the committee in discussing the relation of Government to medicine: the participation of the Government is confined to the economic aspects, and the physician is left in control of the professional relations. The committee therefore endorses this program and recommends its adoption by the New Hampshire Medical Society.

#### *Senate Bill 545*

Committee hearings are now being held on this bill. Proposed by Senators Taft, Smith, Ball and Donnell it would establish a national health agency under which the various health activities of the federal government would be co-ordinated, would provide for the appropriation of \$200,000,000 annually for assistance to the states affording medical, hospital and dental services for low-income patients, with provision for medical and dental examinations of school children and would authorize specific funds for research in cancer and in dental diseases. A significant item in the bill is the permission specifically granted for utilization of nonprofit medical and hospital service plans in providing such care.

Many problems would arise in the administration of such a bill, the most serious one being the method of determining a person's eligibility for assistance. This presumably would have to be handled on the local level, as in relief cases and it would be difficult to avoid the stigma of pauperization.

The committee approves the bill in principle, pending clarification of the details of administration.

L. K. SYCAMORE, *Chairman*  
F. J. C. DUBE  
R. W. ROBINSON

Dr Johnston stated that he understood that administration of the procedures authorized by S 545 was to be left up to the state and local authorities and moved that the Society determine who would be responsible for administration in the state and appoint a committee to take up this problem.

The motion was not seconded.

Dr Sullivan stated that the bill under discussion was definitely socialistic, like other proposals, although it was couched in such terms that its socialistic tendencies were not quite so obvious as those of others proposed in Washington, adding that certainly, the method was clear if one looked into it deeply enough. Supporters of the bill stated that the administration of its provisions would be on the local basis, but the local administration of such a method would ultimately get back to Washington, the location of the head of the organization. He doubted whether any part of this bill were any better than those of any heretofore proposed.

Dr Dye moved that, since the question of clarification was the only controversial point involved, the report be accepted.

This motion was duly seconded.

Dr Richards believed that in trying to avoid federal interference with medicine, which many people considered inevitable, and at the same time voting to approve the bill under discussion, the Society would be acting in a contradictory manner.

Dr Johnston stated that the bill was being passed quickly and that aid would be given to New Hampshire with the implementation of the bill, which was a grant in aid. He agreed that it constituted inter-

ference in medicine, but the bill assumed that local authorities would determine who is indigent. If the motion of Dr. Dye to accept the bill in principle were carried, a whole year would have passed before action, and this bill, in all probability, would have become law by then, the grant in aid to New Hampshire could not be implemented during that period.

The Speaker replied that the bill, of course, did not require endorsement by the Society.

Dr. Sullivan objected to the fact that the report of the Committee on Medical Economics ostensibly pertained to the Blue Cross and Blue Shield organizations in New Hampshire but also concerned the proposed bill in Congress. In other words, the proposal for approval of the committee's report, which comprised accolade for the Blue Cross and Blue Shield, also involved approbation of a socialistic piece of legislation. He thought that the two subjects should be separately discussed.

Dr. Dye stated that if passage of the bill were inevitable, the action of the House of Delegates would not change matters. Although he was opposed to socialized medicine, he understood that the various officers of the American Medical Association and the president of the National Hospital Association and others believed that this bill did not really infringe on the independent rights of physicians. If some sort of socialized medicine could not be avoided, the bill under discussion contained provisions that everybody wants, moreover, it offered an opportunity for local control of its administration. This particular seemed to be the least of a great many evils.

He therefore believed that the committee's report should be accepted, although he agreed that it should be voted on section by section. No definite federalized control of medicine, with compulsory employment of physicians and compulsory payroll deductions for everybody and a sort of panel system of medicine, like that in England, was envisaged in this bill.

The speaker made a point of order that the question before the House was the Senate Bill. Therefore, the motion would have to relate to the bill, rather than to the whole report.

Dr. Dye agreed with this statement.

Dr. Dimerman requested a recapitulation of the highlights of the bill under discussion.

Dr. Dube then read the portion of the report concerning the bill, adding that in his opinion the proposed legislation contained no more social medicine than was already in effect, in the care of the indigent in the towns, except that in the small towns inadequate care is often given. He compared the situation with that of old-age assistance, which could be regarded as a form of social medicine in that the beneficiaries would not receive the care unless the funds were granted in part by the state, town and federal governments. Before the in-

auguration of old-age assistance many older people went without medical care, because some of the town fathers refused to appropriate enough money to take care of these people adequately. The bill under discussion was apparently a grant-in-aid to take care of such cases as could not be cared for locally.

Dr. Feiner inquired whether anyone at the meeting had any knowledge of the reactions of Massachusetts and Vermont and other states to the bill and whether anyone knew how the National Physicians Committee had reacted to the bill. He added that although he believed that socialized medicine was inevitable, the House of Delegates did not have to approve it.

Secretary Metcalf stated that he did not know about the other New England states but that the Taft Bill had been approved by the National Physicians Committee and also by the American Medical Association. Senator Taft, he pointed out, had walked out on the hearings on the Wagner-Murray-Dingell Bill, which he considered to be socialism, and had promised to put in a bill to take the place of that bill. The result was the bill under discussion, which was proposed with the idea of avoiding the extreme socialism of the Wagner-Murray-Dingell Bill and for providing funds for the care of poor people in the different states, to be administered on a local basis. It was pointed out that the federal government had been giving New Hampshire grants for venereal control, tuberculosis control and other items for many years. The proposed legislation was simply an enlargement of what was already being done, as well as a counterattack, on the Wagner-Murray-Dingell Bill, on the assumption that if a bill of this sort goes through, there will be less likelihood of passage of the other legislation.

Dr. Brody observed that the severest critics of the American system of medicine were those who frequently brought up the fact that the indigent were not getting adequate care and that if the proposal legislation offered one way of stopping such critics that was the answer.

Dr. Dye recapitulated the advantages of the proposed bill, which he regarded as meriting approval, at least in principle.

After further discussion, the Speaker put the question, requesting all in favor of approving the report of the Committee on Medical Economics, in relation to S. 545, implying that the House of Delegates approves the bill in principle, with the reservation of desiring further elucidation of the methods of administration, to manifest assent by saying "aye."

There was a chorus of "ayes," with two dissenting votes, and the motion was carried.

The Speaker then pointed out that another item in the report required action — namely, the question of veterans' care by the local physician. He asked Dr. Metcalf to explain the question more fully.

Secretary Metcalf read the portion of his report concerning this subject, adding that, with the agreement and the fee table proposed by the Veterans Administration, he had sent to the secretary of each county society the following letter

A special committee appointed by the House of Delegates has formulated the enclosed agreement and fee schedule, which has been accepted by the Veterans Administration, for the care of veterans with service-connected disabilities. The fee schedule is divided into two parts: care in the home office or hospital outpatient department of veterans with service-connected disabilities and that of veterans with service-connected disabilities as inpatients in hospitals. Many patients in the second group will go directly to a Veterans Administration hospital. Some will be inpatients in a local hospital. The Veterans Administration will not be responsible in either group for medical or surgical bills unless the illness is connected with war service.

All members of the New Hampshire Medical Society are eligible to care for veterans under this agreement at these rates. The members who wish to do so should register with Dr Drury, of Manchester, who will send a copy of the agreement and of the fee table and a letter of instructions.

Please present these data at the next meeting of your county society. If you are not having a regular meeting soon, please consider the advisability of calling a special meeting.

Dr Johnston observed that, in accordance with the letter, most delegates should be instructed by the county societies, and that it was the opinion of his society — Cheshire County — that that portion of the report should be accepted.

On a vote taken, Cheshire, Belknap, Carroll, Grafton and Rockingham counties accepted, and Strafford, Coos and Hillsborough counties rejected the recommendation.

Dr Richards, explaining the rejection by the delegates from Hillsborough County, stated that the vote had not been taken until after a long scientific meeting and that some of the members who had left the room had expected to return and take part in the discussion. The president had wished to rush the matter through. The representatives of Nashua and Manchester had rejected the recommendation. Eighteen people had voted, and over a hundred had been present at the meeting. The Nashua County Society later met and expressed its approval of the recommendation.

The Speaker asked if anyone wished to make a motion.

Dr Dube moved that the House of Delegates go on record as approving the fee schedule as given to the different county societies, as well as the program for the care of the veterans with service-connected disabilities.

This motion was duly seconded.

Dr Dunbar pointed out that Hillsborough County had voted against the acceptance of the Veterans Administration fee list, not against the other proposal.

The Speaker then requested the delegates to signify approval or rejection of the program of home-town care for veterans.

There was a chorus of "ayes," with three dissenting votes, and the motion was carried.

The report of the Committee on Medical Education and Hospitals was then presented, as follows.

The medical educational activities within the Society were practically eliminated as would be expected, during the war period. The extension of fellowships granted us by the Commonwealth Fund in previous years were suspended for the duration and there is no information available as yet regarding the fact or date of their resumption.

The Speakers Bureau — a list of volunteers for the presenting of papers for county meetings and previously available to secretaries of county societies — is long since out of date. The membership — now fairly well stabilized after the war — is again being circulated for re-establishment of this list. It is hoped that this will stimulate some original presentations by our own membership and such a list is welcomed by the county-society secretaries.

In this connection the committee registers its support of the Society's Program Committee in its policy to arouse greater interest on the part of the members in presenting a greater portion of the program of the state meeting than they have in recent years. With the increasing numbers of younger men coming into the state, more emphasis should be placed on this phase of the program. Although prominent outside speakers are a necessary and valuable part of a state-society program, the main purpose should be the presentations of its members. Obviously this can be accomplished only with a real interest and willingness on the part of the members.

There have been many developments in the hospital situation in the past eighteen months — some of which have real significance for the future. This concerns the general implications of the participation of federal funds in hospital construction which will in turn introduce similar participation in hospital standards and thereby perhaps, an indirect participation in a program heretofore assumed to be under purely local control.

In the summer of 1945 as previously reported the Governor of New Hampshire appointed a commission for hospital survey. This followed Senate Resolution 191 which appropriated funds for such a survey in each state. The chairman of this committee served as a member of the commission whose chairman was Mr James Langley, of Concord. The survey carried out by an efficient and experienced field worker, was completed in the fall of 1946, and the report submitted to the Governor.

Two months ago two bills were introduced in the New Hampshire General Court, where they were referred to the Committee on Public Health and Appropriations. These are House Bills No 370 and 371.

House Bill No 371 of the Revised Laws is an act to require the licensing inspection and regulations of hospitals and related institutions. This act could encompass a wide range of activities and would require annual license. The "licensing agency" is the state health officer.

This bill would set up a hospital advisory council to act with the state health officer. It is important that the same council would perform with the New Hampshire Department of Health in the administration of House Bill 370.

Section 10 of House Bill 371 covers the origin of this hospital advisory council as follows:

The Governor with the advice and consent of the council shall appoint an Advisory Hospital Council to advise and consult with the Licensing Agency in carrying out the administration of this act. The Council shall consist of the head of the Licensing Agency (State Health Officer) who shall serve as chairman *ex-officio* and eight other members, and shall include representatives of non-governmental organizations or groups and of state agencies concerned with the operation, construction and utilization of hospitals including representatives of the consumers of hospital services. Each member shall hold office for a term of three years, except that any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term and the terms of office of the members first

taking office shall expire, as designated at the time of appointment, three at the end of the first year, three at the end of the second year and two at the end of the third year after the appointment. Council members shall serve without compensation but shall be entitled to receive actual and necessary travel and subsistence expenses while serving away from their place of residence. The Council shall meet as frequently as the chairman deems necessary, but not less than once each year. Upon request by three or more members, it shall be the duty of the chairman to call a meeting of the Council.

House Bill No. 370 is an act relative to hospital survey and construction. Section 3, on administration, reads as follows:

The Board of Health shall constitute the sole agency of the state for the purpose of (1) making an inventory of existing hospitals, surveying the need for construction of hospitals, and developing a program of hospital construction as provided in sections 6 and 7, and (2) developing and administering a state plan for the construction of public and other nonprofit hospitals as provided in sections 9 and 15 hereof.

The Hospital Advisory Council, as created under Bill 371, is "to advise and consult with the Board of Health in carrying out the administration hereof." The remainder of the bill has to do with procedures of application, review, approval and so forth.

In general, House Bill 370 is the implementation of the Hill-Burton Act for federal aid in hospital construction.

This act will be administered by the United States Public Health Service on a state allocation basis through the agency of the state departments of health. Exhaustive national hospitalization surveys have been carried out by the Public Health Service. Allocation of funds to states will be based on a formula involving population, per-capita wealth and present hospital-bed availability. New Hampshire participation, as based on these factors, will be relatively small — \$340,000 annually for the next five years.

It is assumed that administration of the act will involve practically some direct participation by the federal government by means of the United States Public Health Service in such matters as state boundaries affecting service areas of many of our institutions, which will involve the development of certain intrastate considerations.

Much could be written on the possible implication of this general movement. This is a brief sketch of the factual information.

JOHN P. BOWLER, *Chairman*  
JAMES W. JAMESON  
SAMUEL M. BROOKS

Dr. Macmillan then stated that the Committee on Officers' Reports approved this report and recommended it for consideration.

The motion to accept the report was duly seconded and was carried.

(To be concluded)

## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

#### CASE 33381

##### PRESENTATION OF CASE

A fifty-six-year-old man, formerly a lawyer, who had been employed for the previous seven years as a bartender, was admitted to the hospital with a complaint of weakness.

Eight years prior to admission the patient had noticed edema of the ankles following a venous ligation for varicosities. At about the same time he started drinking heavily, consuming about a quart of liquor a day. For about the same period he had experienced nocturia (two or three times). Six weeks before admission there was a rather sudden onset of dyspnea, which became so troublesome that he had to sleep sitting in a chair. He also became tense and shaky and stopped drinking alcohol after this episode. A physician, who had been giving him vitamins and liver extract for about a year, prescribed Purodign about three weeks prior to entry. On the morning of admission, while still in bed, the patient was seized by a sharp pain

in the left portion of the precordium that was aggravated by deep breathing on moving and relieved after a few hours by the application of heat.

Physical examination revealed a markedly dyspneic man who was slow in comprehending and inaccurate in answering questions. Many purpura spots were present on the arms and abdomen. The skin was pale yellow. There was marked distention of the veins of the neck and legs. The cardiac impulse was felt 11 cm. to the left of the midsternal line in the fifth interspace. A loud apical systolic murmur was heard. The liver edge was palpable three fingerbreadths below the costal margin. There was pitting edema of the ankles.

The temperature was 100°F, and the blood pressure was 130 systolic, 100 diastolic.

Examination of the blood disclosed a red-cell count of 2,520,000, with a hemoglobin of 5.5 gm., and a white-cell count of 21,150, with 76 per cent neutrophils, the hematocrit reading was 24. Several nucleated red cells and macrocytosis and poikilocytosis were noted on the stained smear. Urinalysis revealed a specific gravity of 1.013 with a +++ test for albumin. The sediment contained 30 white cells and rare red cells per high-power field. The total serum protein was 6.1 gm. per 100 cc., with 2.6 gm. of albumin and 3.5 gm. of globulin. The nonprotein nitrogen was 220 mg., the serum calcium 4.6 mg., the phosphorus 12.6 mg., the phosphatase 8.2 units, the cholesterol 250 mg. and the cholesterol esters 151 mg. per 100 cc. The serum chloride was 92 milliequiv., and the serum carbon dioxide 7.1 milliequiv. per liter. The prothrombin time was 42 seconds (normal, 19 seconds). The cephalin-flocculation test was +++ in forty-eight hours. The

van den Bergh reaction was 14 mg per 100 cc direct and 22 mg indirect. A blood Hinton test was negative.

X-ray films of the chest showed generalized enlargement of the cardiac shadow, the ratio being about 15.26. The aorta was somewhat tortuous, and there were mottled areas of increased density extending out into both lung fields from the hilum. A plain film of the abdomen showed kidneys that appeared to be normal in size and position. The liver was somewhat enlarged. No unusual soft-tissue masses were noted, nor were any unusual areas of calcification seen. The visualized portions of the bones appeared normal. An electrocardiogram showed a rate of 75, a PR interval of 0.17 second, normal axis deviation and diphasic T waves in Leads 1 and CF<sub>1</sub>. The T waves were low and upright in Leads 2 and 3 and inverted in Leads CF<sub>4</sub> and CF<sub>6</sub>.

During the first thirty-six hours after admission the patient was practically anuric, passing only 75 cc of urine, and 125 cc was passed during the following twenty-four hours. The nonprotein nitrogen was 180 mg per 100 cc., and the carbon dioxide 11 milliequiv per liter. The patient became weak and vomited several times. On the fourth hospital day he was drowsy and the entire body became edematous. The blood pressure was 133 systolic, 95 diastolic. He expired quietly on the sixth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. JOHN W. ZELLER: When I first read this summary I thought that many of the data given indicated the presence of serious disease of the liver. On considering it further, however, I was more inclined to believe that the patient had declined rapidly because of renal and cardiac disease. Probably the strongest evidences in favor of liver disease are the history of alcohol and the presence of jaundice—I suppose that we can accept the yellow skin as representing jaundice, the record does not state that the scleras were yellow.

DR. BENJAMIN CASTLEMAN: Can you answer that query, Dr. DuToit?

DR. CHARLES H. DUTOIT: The scleras were yellow.

DR. ZELLER: The elevated bilirubin could have been present on the basis of prolonged elevated venous pressure and liver anoxia. According to the history, this condition persisted for no longer than six weeks, which I consider quite time enough for hepatic changes to have developed. There are other data here, however, that could perfectly well go with a diagnosis of severe primary liver disease. The liver was large, although that could be accounted for in other ways. There may have been changes in the vitamin K metabolism as evidenced by the presence of purpura and a prolonged prothrombin time. These findings, however, also occur

in severe renal disease. The anemia could be explained in a clear-cut case on the basis of liver disease. A physician had been giving liver extract for a year previously, possibly with that in mind. The cephalin-flocculation test, of course, in itself is evidence more in favor of hepatic than of renal disease. The test, however, depends on alterations in globulin, which were present in this case and which also occur in renal disease. It alone probably argues somewhat in favor of liver disease. I am willing to concede that the patient had an abnormal liver, but I do not believe that it led to his rapid decline and death.

From the point of view of kidney disease we have the following pertinent data. It is stated that the patient had nocturia two or three times. That does not seem too important in view of the high alcoholic intake. The anemia is consistent with the anemia of prolonged renal disease, which may occur with either a high or a low color index. The urinary findings are not helpful because there was only one urine examination. It is obvious that the service that treated this man had a difficult problem, because he was comatose and not producing urine well and was certainly not a fit subject for adequate study. The high nonprotein nitrogen and the changes in the blood proteins are also consistent with severe renal insufficiency. The high serum phosphorus, the low calcium and the elevated phosphatase are probably the strongest group of findings that argue for primary renal disease of fairly long standing. How long, Dr. Castleman may be able to tell by the appearance of the bones, because if the condition persists for a sufficiently long time, secondary hyperparathyroidism may take place and actual bony changes typical of osteitis fibrosa result. The changes in the serum chloride and carbon dioxide are also consistent. The x-ray studies suggest the presence of pulmonary edema, which certainly would fit in with the picture of some type of cardiac or renal failure.

From the point of view of heart disease, it is evident that the acute episode that marked the beginning of the terminal illness was something that had to do with the heart or lungs. On the morning of admission the patient had chest pain for the first time, described as a sharp, precordial pain on the left side definitely aggravated by deep breathing and moving. It was relieved after a few hours by the application of heat. Certainly, it seems as if there was some pleural involvement, and the implication at the moment is that this man suffered an acute accident involving either the myocardium or the pericardium and the pleura. He showed definite evidence of elevated venous pressure, with distention of the neck veins, a large liver and edema of the legs followed by generalized edema. The cardiac findings themselves are indicative of a large heart.



So far as consideration of the accident that had taken place in the chest goes, there are not many data to help us in making a diagnosis. One wonders about coronary thrombosis. It seems to me that the white-cell count was too high to be explained purely on that basis, although it is a possibility. Any acute abdominal emergency with chest pain is quite unlikely from the rest of the story. We know, however, that in uremia it is possible for events of that sort to occur and not to be clearly defined clinically.

Dissecting aortic aneurysm is rather unlikely, although I was quite attracted to that diagnosis when I thought of the possibility of involvement of the renal arteries and subsequent oliguria. It would not entirely explain the blood chemical findings, however. The summary does not suggest anything resembling spontaneous interstitial pulmonary emphysema. Pulmonary infarction must be considered. This man had a prolonged prothrombin time, and the veins had been tied off eight years previously. We know that there are some disquieting cases in which venous ligation has failed to prevent pulmonary emboli, but I doubt whether that occurred in this patient.

Other conditions that sometimes occur in patients in terminal uremia are pericarditis with effusion or even septic pericarditis. In this particular case I believe that pericarditis may adequately explain the findings. The rapid onset of dyspnea about six weeks before admission might seem difficult to explain in this way, but cases of pericarditis with effusion and a fairly rapid onset of dyspnea occur. The pain on admission could have been due to pericarditis with some associated pleural involvement. I hope that the x-ray films will give some help on that.

So far as the blood pressure is concerned, a pressure of sufficient degree was maintained to make me doubtful about the presence of coronary thrombosis.

May I see the temperature chart? In the written abstract only one temperature reading of 100°F is recorded. I should have expected a slightly higher temperature with a septic process. None are recorded, and the chart shows a gradual descent during the last three days in the hospital. The fact that the pulse came down is also interesting and is against the presence of uncomplicated myocardial failure. The respirations were steady — around 20 — until they went up to a high figure shortly before death. It should again be pointed out that sometimes the temperature does not indicate the presence of sepsis in debilitated patients with uremia.

May we see the x-ray films?

DR STANLEY M. WYMAN: The enlargement of the heart described is well seen. I cannot say that it is a characteristic configuration. It might be due to pericarditis.

DR ZELLER: Were the films taken in a recumbent position?

DR WYMAN: No, the patient was upright.

There is no evidence of a large effusion in the pleural cavity, but I strongly suspect a small amount of fluid in each costophrenic angle. The mottled density in both lung fields seems to emanate from the hili and is patchy in character, suggesting edema.

The record states that in the film of the abdomen the kidneys are normal in size and shape. I believe that they are small and also that they are irregular in contour, suggesting lobulation. The liver may be large. The spleen I cannot make out. Dr Zeller raised the question of bone changes, and I might say that the bones do look osteoporotic.

DR ZELLER: That is a real help.

I do not feel like commenting to any great extent on the electrocardiogram. The findings are not particularly indicative of coronary thrombosis. The absence of Q waves is against it. The T-wave changes are consistent with a diagnosis of pericarditis.

DR DUToIT: I might add that a pericardial friction rub was heard.

DR ZELLER: That is also helpful. Is there any other information that I should have?

DR DUToIT: No.

DR ZELLER: From the point of view of the underlying renal disease, we now have an x-ray interpretation that indicates the presence of shrunken kidneys of some sort. So far as polycystic disease is concerned, I should not expect the kidneys to be shrunken and polycystic at the same time. Polycystic kidneys are usually fairly large. I should prefer to consider the presence of chronic glomerulonephritis, chronic vascular nephritis or pyelonephritis, with this picture as an end result. I doubt that the underlying disease was renal tuberculosis or some of the more definite urologic conditions with obstruction, ureteral or prostatic. In such a case I think that more definite information regarding such an obstruction would have been available during the patient's life.

DR DUToIT: The patient was catheterized, and 75 cc of urine was obtained.

DR ZELLER: I rather doubt that the patient had an end stage of amyloid disease of the kidneys. I do not know on what basis it could occur. I have not heard of its occurring with cirrhosis of the liver.

For my final diagnosis I shall have to say that the patient had severe, diffuse, long-standing renal disease — probably chronic glomerulonephritis or chronic vascular nephritis — and pericarditis with effusion. The effusion may have been associated with some bleeding into the pericardium, which has often been described. I rather doubt that it was hemorrhage into the pericardium, however. I originally suspected a septic pericarditis, but since see-

ing the temperature chart, I am less impressed with that possibility. I also believe that this patient had pulmonary edema and secondary hyperparathyroidism, with evidence of osteitis fibrosa in the bones. I think that it is entirely likely that he had the alcoholic type of cirrhosis of the liver.

DR. WILLIAM W. BECKMAN: Do you care to comment on the blood smear? That bewildered us on the ward.

DR. ZELLER: I can comment to the extent of saying that I too am bewildered by it. I think that a smear of this sort can be associated with the anemia of severe liver disease. I was unable, actually, to find a description of anything like this to fit the picture of anemia associated with severe renal disease. If I were forced to say, I think that it is more consistent with severe liver disease than renal disease.

DR. JACOB LERMAN: The blood picture indicates bone-marrow invasion or blood loss.

DR. DUROI: Dr. Wyman Richardson saw the blood smear and said that it was suggestive of bone-marrow invasion such as multiple myeloma.

DR. BECKMAN: Was Bence-Jones protein found?

DR. DUROI: We were unable to find any by crude test.

#### CLINICAL DIAGNOSES

Uremia, due to chronic glomerulonephritis  
Hypertensive heart disease, with failure  
Portal cirrhosis of liver

#### DR. ZELLER'S DIAGNOSES

Severe, diffuse, long-standing renal disease  
(? chronic glomerulonephritis or chronic vascular nephritis)

Uremia  
Pericarditis, with effusion  
Pulmonary edema  
Secondary hyperparathyroidism

#### ANATOMICAL DIAGNOSES

Acute and chronic pyelonephritis  
Pericarditis, acute, fibrinous, uremic  
Cardiac hypertrophy  
Pulmonary congestion and edema  
Central congestion and necrosis of liver  
Hydrothorax, bilateral, slight  
Ascites, slight  
Parathyroid hyperplasia, secondary

#### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Autopsy showed an enlarged heart that weighed over 400 gm. There was pericarditis of the fibrinous type, with a little effusion — 75 cc of turbid fluid — but no sepsis. I believe that it is rare to find septic pericarditis associated with uremia. One sees thick fibrin described as the bread-and-butter type, but cultures are almost always sterile. The coronary arteries were not remarkable.

The kidneys were shrunken, weighing together 150 gm. They showed slight to moderate lobulation, the surface of the kidney between the scars being fairly smooth rather than coarsely granular. At the time of autopsy there were a number of wagers going on regarding what type of renal disease was present. The facts that the kidneys were lobulated and contained yellow areas and that the intervening parenchyma was smooth made one group think that it was chronic pyelonephritis, and another group considered it vascular nephritis, and a third group, glomerulonephritis. Microscopical sections, however, revealed some degree of vascular change, but there was marked fibrosis and cellular infiltration throughout the kidneys, both chronic and acute. I believe that the whole process is best explained by chronic pyelonephritis, with some activity still going on. As a result of the long-standing renal disease there was secondary hyperplasia of the parathyroid glands. The bones showed a few areas of early bone resorption such as one might see in long-standing renal disease. The lungs were heavy, weighing over 1000 gm, and showed a fair amount of congestion and some edema. The liver was not enlarged, weighed 1400 gm and on microscopical section showed a severe degree of central necrosis and congestion, such as one might see with failure of the right side of the heart, that is consistent with the engorgement of the neck veins, the pleural fluid — 200 cc in each pleural cavity — and the ascites.

DR. BECKMAN: How about the bone marrow?

DR. CASTLEMAN: The bone marrow showed moderate red-cell hyperplasia.

#### CASE 33382

#### PRESENTATION OF CASE

A sixty-year-old nulliparous housewife entered the hospital with the chief complaint of weakness.

Six months before entry the patient had been admitted to another hospital complaining of weakness, nervousness and weight loss of unknown amount. She had had asthma for four years. The thyroid gland was somewhat enlarged, and the pulse was about 110. The basal metabolic rate was recorded at +40 per cent. An eosinophilia of 11 to 19 per cent was present. A thyroidectomy was advised, but the patient desired to delay the operation. Four months later, after being on iodine therapy, she was readmitted, and a subtotal thyroidectomy performed. The pathological report was "colloid goiter with no evidence of hyperplasia." Postoperatively, she was improved until ten days after discharge, when she awoke at 2:00 a.m. with "heaviness" of the right arm. This was followed in a few days by similar sensations in the left arm, the right leg and, finally, the left leg. Weakness

followed, and she became bedridden. Vitamin B injections did not help. No dysphagia was noted. Dyspnea and orthopnea became increasingly severe. No cough, chest pain or gastrointestinal symptoms were observed. Some mental deterioration had occurred gradually during the preceding two years. The patient had had nocturia (four times) without other genitourinary symptoms for several months. The menopause had occurred at the age of fifty-four years.

Physical examination revealed an emaciated, orthopneic woman with soft atrophic muscles. There was dependent edema of the arms, legs and sacrum. The heart rate was regular, with sounds of poor quality. The heart was not enlarged. There was flatness to percussion over the lower right portion of the chest, with diminished breath sounds but no rales. The liver edge was palpated four fingerbreadths below the costal margin. The abdomen was normal otherwise. The pupils and ocular movements were normal. There was no facial weakness. The palate and tongue were normal. Except for slight movement at the shoulder, there was complete paralysis of the right arm and hand. The strength of the left arm and hand was about a fourth normal. The dorsiflexors of both feet were paralyzed, there was little voluntary movement of the right leg, the left leg was somewhat stronger and could be raised voluntarily. The arm jerks were present on the right and absent on the left side, and the knee and ankle jerks were absent, as were the plantar reflexes. Because of the patient's mental status sensory examination was not satisfactory. Pinprick and touch were recognized everywhere but seemed to be diminished over the extremities. Vibration was felt at the wrists but not over the tibiae and malleoli. There did not seem to be a sensory level. A healed thyroidectomy scar was present.

The temperature was 98.6°F, the pulse 120, the respirations 50, and the blood pressure 115 systolic, 75 diastolic.

Examination of the blood disclosed a white-cell count of 33,900, with 38 per cent eosinophils, 4 per cent lymphocytes, 4 per cent monocytes and 54 per cent neutrophils. The urine had a specific gravity of 1.018 and gave a ++ test for albumin but contained no sugar. Four red cells, 6 white cells and a rare granular cast per high-power field were present in the sediment. The urine culture showed colon bacilli and nonhemolytic streptococci. The total protein was 5.84 gm. per 100 cc., with an albumin-globulin ratio of 0.85. The nonprotein nitrogen was 35 mg. per 100 cc. An electrocardiogram showed a normal axis, the T waves were extremely low in Lead I, flat in Leads 2 and 3 and upright in Lead CF<sub>2</sub>. On the next day auricular fibrillation was noted.

X-ray studies showed moderate decalcification of the spine, an area of homogeneous density at the

right base having the appearance of pleural fluid and a calcified area in the region of the right lobe of the thyroid gland.

The patient continued to suffer from dyspnea and orthopnea in spite of digitalis and oxygen. She became aphasic and disoriented and died on the sixth hospital day.

### DIFFERENTIAL DIAGNOSIS

DR WILLIAM CLARK. It is not quite clear to me when the patient was admitted to this hospital, but I am assuming that it was about one and a half months after the onset of the sensation of heaviness in the right arm. I should like to separate the course of the illness into three phases, the first being characterized by asthma, the second by weakness, nervousness and loss of weight, and the third by neurologic, cardiac and renal disease. It seems reasonable to me, however, that one dominant pathologic process was responsible for all the manifestations and that the asthma was the first symptom. During the course of this illness a diagnosis of thyrotoxicosis was made, and a subtotal thyroidectomy was performed. In retrospect I believe that it is justifiable to question the diagnosis of hyperthyroidism in spite of the fact that it seemed a logical explanation for the weakness, nervousness, loss of weight and tachycardia prior to operation. Even in the presence of an elevated basal metabolic rate we know that such phenomena are common to many diseases, and fitting all three phases together will give us a more logical explanation for the preoperative symptoms.

The pathologist's report and the postoperative course make the diagnosis of thyrotoxicosis somewhat questionable. Some evidence of hyperplasia should have been found. It is my impression that complete involution of the thyroid gland is not the rule following iodine therapy. Extreme muscle weakness is sometimes encountered on the basis of Graves's disease, even after thyroidectomy, particularly when a large portion of the gland functions outside the neck and is not seen by the surgeon. I prefer to believe, however, that the patient did not have Graves's disease. During the early phases of the illness one might become immediately suspicious of periarteritis nodosa as a possible diagnosis because of the asthma and eosinophilia. The association of these two diseases has been pointed out by Dr. Francis M. Rackemann.\* After the operation the patient seemed to have developed a neurologic disease and, in addition, presented fairly definite evidence of involvement of the heart and kidneys. I am referring, of course, to the orthopnea and dyspnea, pleural effusion, hepatomegaly and dependent edema in reference to the heart and to the urinary findings in reference to the kidneys. I shall

\*Rackemann, F. M., and Greene, J. E. Periarteritis nodosa and asthma. *Tr. A. Am. Physicians* 54: 112-118, 1939.

pass over the nervous-system involvement for a moment to make some remarks about the involvement of these two systems. Some of the respiratory distress may have been related to the asthma, although wheezing is not mentioned. The low serum protein may have played a role in the edema and may have been related to the liver disease. The pleural effusion could have been a manifestation of heart failure but also may have been associated with serositis. The renal disease consisted of albuminuria and cells in the sediment and perhaps the additional findings of a slight elevation of the nonprotein nitrogen and lowering of the serum protein. I note that there was no hypertension, and I should not consider the renal disease the primary factor.

Without going in detail into the findings in the examination of the nervous system, I shall assume that the only logical explanation is that a polyneuritis developed. The involvement was bilateral and somewhat bizarre, with rather definite sensory involvement.

Such neurologic manifestations are so frequently associated with periarthritis nodosa, occurring in the presence of asthma and a high eosinophilia, that they make such a diagnosis almost compelling. I shall attribute all the manifestations of the illness to a generalized necrotizing arteritis. Other causes of eosinophilia do not seem to fit well, and I shall not discuss them. Some criticism of the diagnosis of periarthritis nodosa may be justified on the basis of the lack of fever and hypertension, but we know that these findings are not always present. Periarthritis nodosa has strange manifestations, and tissue examination is almost always necessary to establish its presence. I should think that tissue removed at the thyroidectomy would not have been helpful in this regard. In addition, postmenopausal osteoporosis and generalized atherosclerosis were probably present, and the latter may have contributed to both the mental confusion and the heart disease.

Dr. ALFRED KRAMER. I was asked to see this patient after an episode of acute peripheral circulatory collapse characterized by marked tachycardia, a fall in blood pressure, sweating and dyspnea. It was at first thought that this represented an idiosyncrasy to barbiturates because a similar episode had occurred postoperatively, when barbiturates had been administered. Additional information in the history, however, ruled this factor out, since it was discovered that the patient had been taking these drugs intermittently for some time.

She was not more extensively studied because during her stay here she remained critically ill. I reached exactly the same conclusion that Dr. Clark did, believing that periarthritis nodosa was the best explanation for the complicated picture presented.

## CLINICAL DIAGNOSIS

Periarthritis nodosa

## Dr. CLARK's DIAGNOSES

Periarthritis nodosa

Pleural effusion

## ANATOMICAL DIAGNOSES

Periarthritis nodosa

Hydrothorax, bilateral

Pericarditis, acute fibrinous

## PATHOLOGICAL DISCUSSION

Dr. BENJAMIN CASTLEMAN. The diagnosis of periarthritis nodosa is not usually made grossly at autopsy because in most cases the involved vessels are arterioles and small arteries. It is only when the lesions are present in the larger arteries, such as the coronary and the mesenteric, that one can palpate or see the nodularity and beading of the vessel wall. In this case the only suggestive gross findings were some scattered whitish areas in the cortex of the kidneys and a yellowish spot in the interventricular septum. Microscopically, these foci proved to be small infarcts resulting from occluded diseased vessels. All stages of arteritis from acute necrosis of the vessel walls with polymorphonuclear—especially eosinophilic—infiltration to organization of thrombi with recanalization were seen in the heart, kidneys, liver, peripheral nerves and skeletal muscles.

The thyroid gland showed no evidence of hyperplasia or arterial disease. I was unable to find any arteritis in the lungs, but the bronchi contained a great deal of mucus and the basement membranes and muscle walls of the bronchi appeared thicker than normal. These findings are consistent with bronchial asthma.

Dr. KUBIK will tell us about the neurologic findings.

Dr. CHARLES S. KUBIK. When I saw the patient on admission the history of a sudden onset of the weakness of the right arm suggested a vascular lesion. The extent and nature of the motor and sensory involvement pointed to multiple lesions, and that together with a history of asthma, indications of cardiac disease and the presence of eosinophilia made the diagnosis of periarthritis nodosa extremely likely.

At autopsy nothing abnormal was observed in the brain, brain stem, spinal cord or peripheral nerves.

On microscopic examination there was arteritis involving a medium-sized subarachnoid artery of the medulla, although the medulla itself and the vessels within it were normal. In the middle and lower cervical regions of the spinal cord, at two neighboring levels, there were similarly diseased, small sub-

arachnoid arteries in the anterior, median fissure. One of these was probably occluded by thrombosis. There were no indications of infarction or signs of ischemia within the cord at these or other levels. The spinal nerves throughout were normal, and nothing abnormal was found in the cerebrum. The only abnormal finding observed within the central nervous system was axonal reaction of the anterior-horn cells of the cervical and lumbosacral regions of the spinal cord. This change, consisting of swelling and central chromatolysis, is characteristic of peripheral-nerve disease, and the reason for it in this case was quite obvious. There was extensive

arteritis involving the small arteries of the peripheral nerves. None of the affected vessels were thrombosed. There was no actual degeneration of the nerve fibers, the myelin sheaths, although probably slightly abnormal, were essentially intact. It is interesting that there may be a marked axonal reaction even though visible changes in the nerve fibers are slight. The same thing has been true in some cases of infectious polyneuritis.

In the cases of periarteritis nodosa examined here, lesions of the nervous system have not been frequent. I recall another case in which there was severe disease of the peripheral nerves and at least one in which there were lesions of the brain.

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## COST OF HOSPITAL CARE

THE cost of hospital care, together with that of many necessities of life, has increased to a point where it can be met without sacrifice by only a small portion of the population. This is not surprising when it is realized that even in 1942, a war year, the average income of 84 per cent of the workers in Massachusetts was less than \$3000 a year.<sup>1</sup> Two additional factors contribute to the difficulty: there is an acute shortage of hospital beds, and more and more people, owing to modern advances in the detection of such diseases as cancer, diabetes, nephritis and tuberculosis, require hospitalization. It is true that the cost of hospitalization can be completely or partially covered by enrollment in a prepayment insurance plan, but even the Blue Cross appears to be having trouble

in meeting its obligations. Furthermore, although a patient is entitled to receive or able to pay for hospitalization, it is often impossible to secure a hospital bed, even in cases of emergency. The question arises, What can be done to relieve this situation?

In the first place, steps should be taken to increase screening tests whereby disease is detected before it has advanced to a stage that requires hospitalization and to educate the public regarding the symptoms and signs of various slowly progressive diseases. Much has already been accomplished along these lines in tuberculosis and diabetes, but a great deal remains to be done, both in these diseases and in others.

Secondly, certain types of patients should be encouraged, during the period of study and treatment, to remain in their homes or to take up residence in nursing homes, hotels and boarding houses. This ambulatory type of care is less expensive than hospitalization and can be conducted satisfactorily provided that adequate supervision is maintained by means of office visits or by attendance at outpatient clinics. In the latter, and occasionally in doctors' offices, group instruction offers an inexpensive type of medical care, having proved particularly effective in patients with tuberculosis, neuropsychiatric disorders and diabetes.

Thirdly, as previously mentioned in this column,<sup>2</sup> hospitals should be urged, at least while the acute shortage of hospital beds exists, to operate on a seven-day week, with service available in operating rooms, x-ray departments and laboratories. This would not only increase the number of available beds but also cut down somewhat on the per-diem cost, owing to the decrease in overhead charges that accompanies operation at full capacity. Furthermore, if personnel were available for this type of service, hospital care could be provided by existing hospitals at a lower cost per patient than could be attained by the construction of new hospitals.

Fourthly, when the patient has been admitted to the hospital, it should be the duty of the attending physician to limit hospital services to the indispensable minimum consistent with adequate study and care, to expedite treatment and to discharge the patient at the earliest possible moment that is

compatible with health. One hospital in Boston has adopted a plan whereby the total hospital charges of diabetic patients requiring medical and surgical care who were discharged during the previous week are shown at the staff visit each Monday. A typical sheet lists twelve ward and semiprivate patients with an average total charge of \$269, exclusive of doctors' fees. Such a procedure should accomplish much in impressing on the physician the need for decision and action.

Finally, it is to be hoped that in the not too distant future the costs of the supplies and equipment that are essential to hospitals will drop to a reasonable figure. Just when this will occur, however, is a question on which the ablest economists refuse to hazard a guess. That this is the chief factor in the cost of hospital care is indicated by the fact that the cost of food, clothing, shelter, fuel and light has risen from a combined index number of 98 in 1941 to one of 149 in 1947.

Hospital costs, as well as the expenses of medical care, must be placed within the reach of all. Only with the co-operative efforts of physicians, hospitals, public-health agencies, organizations underwriting prepayment insurance and government — through full payment for services rendered to the indigent — can this goal be attained.

#### REFERENCES

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2. Editorial. Full utilization of hospital facilities. *New Eng J Med* 236:767, 1947.

### EPIDEMIOLOGY OF POLIOMYELITIS

ABOUT a year ago there was some discussion regarding the propriety and justification of criticisms in the lay press directed against the manner in which the public-health aspects of infantile paralysis were handled in one of Boston's suburbs.<sup>1</sup> This was merely one reflection of the limited knowledge concerning the causes of epidemics of this disease, the manner in which the causative virus spreads and the efficacy of measures intended to control its spread.

In a recent paper read at the Rocky Mountain Conference on Infantile Paralysis, Sabin<sup>2</sup> summarized some of the recent contributions to the knowledge of the epidemiology of poliomyelitis. His paper,

in its published form, includes an appropriate and timely addendum in which he presents certain guiding principles that are suggested by the facts thus far accumulated. Practical public-health measures are then offered that are in accord with these principles. These suggestions should be helpful to health officers confronted with an outbreak of this disease.

Reduced to its barest essentials, the epidemiology of poliomyelitis may be considered to be similar to that of other enteric infections in which the causative virus is much more widely disseminated in the community during an epidemic than at other times. The care of patients and the public-health measures should therefore be directed toward limiting contact with and the spread of the virus. It has been shown that this virus is present for only a short time in the throat and more frequently and for a longer time in the intestinal tract and stools of certain apparently healthy people, as well as those of nonparalytic and paralytic cases during the epidemic. The virus may be transmitted to others by intimate contact, contaminated hands and fomites. Spread by the respiratory tract seems to play little if any role. The "filth" flies, however, can be contaminated with the virus and may spread it on to food in infective amounts. On the other hand, there is no evidence that the disease is spread by blood-sucking insects, since the virus is rarely found in the blood.

Some of the specific practical suggestions that Sabin offers in answer to the questions most frequently put to health authorities may be mentioned briefly as follows.

Measures designed to minimize spread by droplet infection do not seem to be warranted. It should therefore not be necessary to close motion-picture houses or churches or to refuse admission of patients with poliomyelitis to general-hospital wards.

The closing of playgrounds, swimming pools and other places where children come into direct contact with one another seems justified. The closing of schools depends on whether it is possible better to avoid contact between children in or out of school. Strenuous exercises are best

avoided during an epidemic, particularly by those who have had known and intimate exposure

As to insect control, measures designed to minimize the contamination of food by flies in stores and in homes and efforts directed at the prevention of the breeding of flies where there may be any exposed sewage are warranted. The mass spraying of whole towns or communities with DDT, on the other hand, is of doubtful value.

Patients with poliomyelitis may be cared for on the wards of general hospitals provided that precautions similar to those used in caring for patients with typhoid fever are carried out, including the handling of their food, linens and excreta.

At home, patients with poliomyelitis should be isolated for at least two weeks, and even an isolation period of four weeks, dating from the first onset of symptoms, seems reasonable. The children of such households and the older members who are engaged in the handling of food in stores or restaurants or whose occupations bring them in intimate contact with children should remain at home for a period of at least two weeks. The same procedure is advocated for children who have been exposed in intimate play with members of an infected household.

Sabin emphasizes repeatedly that all these measures will probably not stop an epidemic, but in so far as they are carried out diligently, they may help at least some persons to escape infection who might otherwise be paralyzed.

It is to be borne in mind, however, that these conclusions and recommendations are based on Sabin's own interpretations of the results of recent experimental and epidemiologic studies. Other interpretations of the same findings are apparently possible and may cause some confusion in the minds of public-health workers. Dauer,<sup>3</sup> for example, concludes that the spread of the virus is probably through secretions of the oropharynx. His conclusion is based on the observations of a number of investigators that transmission of infection takes place in the interval between a few days before and a few days after the onset of a case, coupled with the fact that the virus has been recovered from

oropharyngeal secretions in a large proportion of cases not longer than four or five days following the onset.

#### REFERENCES

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- 2 Sabin A B. Epidemiology of poliomyelitis: problems at home and among armed forces abroad. *J A M A* 124 749-756, 1947.
- 3 Dauer C C. Incidence of poliomyelitis in 1946. *Pub Health Rep.* 62:901-907 1947.

#### NEW HAMPSHIRE MEDICAL SOCIETY

##### DEATH

SIKORSKY — Vladimir N Sikorsky M.D., formerly of North Hampton, died on August 1. He was in his eighty-first year.

Dr. Sikorsky recently received a medal for fifty years of membership in the New Hampshire Medical Society. Two daughters survive.

#### BOOK REVIEWS

*Penicillin in Syphilis*. By Joseph E. Moore, M.D. 8", cloth, 319 pp., with 57 illustrations and 52 tables. Springfield, Illinois: Charles C Thomas 1946. \$5.00.

This book is almost as much a contribution to all general phases of medicine in which penicillin is used as it is an exposition of the specific treatment of syphilis. Anyone wishing to learn something about pharmacology and biology of penicillin can well spend his time with this concise analysis and interpretation of the work of the author, that of his immediate colleagues and that of the associated group studies. Slightly more than a third of the volume concerns the basic knowledge of penicillin; the rest deals with special problems of syphilis and how to combat them with penicillin.

Penicillin like other specific antisyphilitic drugs is capable of producing shock (the so-called "Herxheimer reaction") and in early syphilis these reactions occur in at least 60 to 70 per cent of cases. Unlike the metallic drugs however, there is no treatment fastness to penicillin. The danger of suppressive doses — as compared with total therapeutic doses — when penicillin is used for treatment of the disease associated with unrecognized early syphilis, is elaborately discussed. There is an excellent exposition of the relation between the time and dosage factors in the over all treatment schedule. This important phase of the treatment of syphilis, which is well known to the syphilologist, is clearly expounded for those who will read carefully.

Weight for weight, penicillin is from two to four times as effective as Mapharsen in the therapy of syphilis in man. Its greatest effectiveness is in early syphilis during the phase of the infection when the spirochetes are in their most active dividing phases. With an aqueous solution a total dosage of 2,400,000 units divided into sixty injections in seven and a half days, seems to be the best schedule for early active cases. It is strongly hinted although not vigorously proposed that ten daily single injections of 600,000 units of penicillin in peanut oil and beeswax is an even more effective schedule.

Gummas respond rapidly to penicillin, seroreactivity of latent syphilis is not so responsive. Penicillin is so dramatically effective in preventing congenital syphilis that metallic therapy should be completely and universally replaced by penicillin therapy in pregnancy. The effect is equally dramatic in the management of the infant with congenital syphilis. In cerebrospinal syphilis, penicillin in addition to fever therapy is superior to all other treatment alone, it is as effective as metal and fever therapy and is superior to any metal alone.

This small book is packed with information for the student of syphilis and contains essential material for those who treat syphilis.

*Radiology for Medical Students*. By Fred J. Hodges, M.D., Isadore Lampe, M.D. and John F. Holt, M.D. 8", cloth 424 pp. with 103 plates. Chicago: The Year Book Publishers Incorporated 1947. \$6.75.

This monograph offers a basic approach to the problem of x-ray diagnosis and therapy without attempting to provide



details in all the ramifications of radiology. The authors provide only a short discussion of the theory of the roentgen ray and brief descriptions of the apparatus, enough to make the theoretical concepts understandable. The technique of obtaining films are discussed only from the point of view of what one can expect to gain from the usual views of each region. The object of the book is not to make a roentgenologist out of each medical student who reads it, but rather to give him enough knowledge so that no matter whether he becomes a general practitioner or a specialist in any field, he will be able to utilize x-ray technic to its full extent and at the same time to recognize its inevitable limitations. The illustrations are ample in number and excellent in quality and follow along with the text so that they are easily available for study. About a third of the text is devoted to radiation therapy, which is rarely discussed in specific detail, rather, space is devoted to the general theoretical and clinical principles involved. For those who desire further information on any subject, an excellent bibliography follows each chapter. This is a book that every medical student would do well to own.

*Whether Medicine From dogma to science?* By Antony Fidler, M.D. 12°, cloth, 115 pp. Edinburgh Thomas Nelson and Sons, Ltd., 1946. 6 sh.

In this monograph the author, who is a docent of medicine of the University of Warsaw and is at present senior lecturer in medicine at the Polish School of Medicine in Edinburgh, offers a philosophical criticism and evaluation of the present scheme of what he terms "causal medicine." As an alternative, he suggests a system of diagnosis, prognosis and treatment called "the medicine of probability," based on analysis, by the experimental method, of comparative data from large groups of cases. He illustrates the application of this new scheme in medicine by examination of several thousand cases in seven tables in an appendix. His concept, contention and method seem those of the statistician rather than those of the clinician or physician, his paradoxical theory is interesting, but not immediately convincing. It may be questioned whether the medicine of probability would really be more scientific than causal medicine. Perhaps, in spite of the author's statements, medicine is still more an art than an exact science. He himself agrees that "the strength of the personal impressions of a physician grows with his experience, and that is perhaps why older physicians are more inclined to rely upon their clinical 'flair' than upon the results of laboratory findings, and it must be admitted that they are less often mistaken as to their patients' fate than those who place their faith in the findings of the laboratory."

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Charles Darwin and the Voyage of the Beagle*. Edited by Nora Barlow. 8°, cloth, 279 pp., with twelve plates, 1 portrait and 1 map. New York Philosophical Library, 1946. \$3.75.

This biographical study is based on twenty-four small, informal unpublished notebooks of Darwin, and thirty-nine letters written by Darwin to his father and sisters, here published in their entirety for the first time. Eight of the letters were previously published in part in the *Life and Letters of Charles Darwin*, by Francis Darwin.

The first part is a short sketch of the life of Darwin, dealing especially with the incidents leading up to his joining of the *Beagle* expedition. The second part comprises the letters and notebooks. These personal notebooks, written mostly after working hours, throw an interesting light on Darwin's processes of thought. A good index concludes the volume.

*Proceedings of the Charaka Club*. Volume XI. 8°, cloth, 243 pp. New York Richard R. Smith, 1947. \$7.00.

This new volume contains a selection of papers read before the club during the years 1940 to 1944. Boston physicians are represented by five papers by Dr. Fred B. Lund, one in

conjunction with Dr. Cecil K. Drinker. Lists of present and past members and unpublished material precede the papers. A number of the contributions are short biographical sketches of deceased members, including George L. Walton, by Dr. Lund, and Walter R. Steiner, by Dr. Rufus Cole.

*Surgical Pathology*. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), LL.D., F.R.S.C., professor of pathology, University of Toronto. Sixth edition. 8°, cloth, 858 pp., with 530 illustrations, including 22 in color. Philadelphia W. B. Saunders Company, 1947. \$10.00.

This authoritative textbook, first published in 1925 and last revised in 1942, has again been revised. A new section has been added on the pathology and pathologic physiology of congenital heart disease. New material includes tumors of the larynx, pinealoma, Bittner's milk factor in relation to breast cancer, avitaminosis in cancer of the mouth, the Papanicolaou vaginal-smear method in the diagnosis of carcinoma of the cervix, fibrous dysplasia of bone, inflammatory nodules in chronic arthritis and fibrositis of the back. The book is recommended for all medical libraries and as a standard text on the subject.

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, SEPTEMBER 25

FRIDAY, SEPTEMBER 26

\*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, SEPTEMBER 29

\*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, SEPTEMBER 30

\*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY, OCTOBER 1

\*12:00 m. Grand Rounds' and Clinicopathological Conference. (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital.

\*Open to the medical profession.

SEPTEMBER 23. Norfolk District Medical Society. Page 382, issue of September 4.

OCTOBER 3 AND 4. New York Academy of Sciences. Page 348, issue of August 28.

OCTOBER 6-10. American Public Health Association. Page 456, issue of March 20.

OCTOBER 6-17. New York Academy of Medicine. Page 348, issue of August 28.

OCTOBER 9. Practical Points in Geriatrics. Dr. Roger I. Lee. Foulmouth Association of Physicians. 8:30 p.m. Haverhill.

OCTOBER-DECEMBER. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 28.

OCTOBER 13-18. Medical Conference and Seminar for Pathologists, Medical Examiners and Coroners. Page 242, issue of August 14.

OCTOBER 29-31. New England Postgraduate Assembly. Copley Plaza Hotel, Boston.

FEBRUARY 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

APRIL 19-23. American College of Physicians. Page xiii, issue of July 31.

MAY 6-8. American Association for the Study of Goiter. Page xiii, issue of July 31.

MAY 11-15. American Association on Mental Deficiency. Page 140, issue of July 24.

### DISTRICT MEDICAL SOCIETIES

#### MIDDLESEX EAST

SEPTEMBER 24

NOVEMBER 19

JANUARY 21

MARCH 24

MAY 12. Annual meeting.

All meetings will be held at the Bear Hill Golf Club.

#### NORFOLK

SEPTEMBER 23. Boston University Night.

OCTOBER 28. Lahey Clinic Night.

NOVEMBER 25. Tufts Night.

JANUARY 27. Round-Table Discussion. Bleeding from the Alimentary Tract.

FEBRUARY 24. Obstetric and Gynecologic Night.

MARCH 23. Harvard Night.

(Notices continued on page viii)

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## PRESENTATION OF THE HENRY JACOB BIGELOW GOLD MEDAL

### INTRODUCTORY REMARKS AND PRESENTATION OF THE MEDAL\*

JOE V MEIGS, M D †

BOSTON

THIS evening we meet to do honor to one of our own Elliott Carr Cutler received his degree in 1913 from Harvard Medical School, where he was a member of the Boylston Medical Society, Alpha Omega Alpha Society and the Aesculapian Club. Thus, characteristically, at the start of his medical career he was a member of the school's literary society, its honor society and its social society. After graduation he went to the Peter Bent Brigham Hospital as surgical house officer. Before the United States entered World War I he was a member of the Harvard Unit, serving with the British Army. On his return to this country he served as resident surgeon at the Massachusetts General Hospital. He then became alumni assistant in surgery at Harvard Medical School and voluntary assistant to the Rockefeller Institute of New York. When the United States entered World War I he joined the Medical Corps of the Army, starting as a lieutenant, but as might have been expected, he was later promoted to captain and then to major. At the end of his military career in the Army, he became resident surgeon at the Peter Bent Brigham Hospital, serving from 1919 to 1921. He subsequently became an associate in surgery at Harvard Medical School. In 1924 he accepted a call to the professorship of surgery at Western Reserve University School of Medicine and was also appointed director of the Surgical Service of the Lakeside Hospital. Here he served with distinction, and one has only to inquire of those who knew him in Cleveland to hear of the great changes and advances that he wrought while there. In 1932, on the retirement of his former chief, the great Dr. Harvey Cushing, he was called back to Harvard Medical School to become Moseley Professor of Surgery and surgeon-in-chief at the Peter Bent Brigham Hospital. It was during that time that

he advanced the knowledge of surgery of the heart by his work on the thyroid gland and its relation to heart failure and by the first operation done directly on the valves of the heart to relieve the crippling effects of mitral stenosis. At the Peter Bent Brigham Hospital he produced much original work, but even greater and more lasting than his scientific contributions was his influence on the young surgeons who were so fortunate as to be trained under him. His enthusiasm and his dynamic personality, as well as his profound knowledge of surgery, left their mark on all his students.

In the summer of 1940, immediately after the fall of France, he reorganized Harvard University Base Hospital No. 5. He was farsighted enough to see that in 1940 we had best be prepared. It was natural that with the outbreak of World War II he should have been appointed by the Governor of the Commonwealth as director of the Medical Division of the Massachusetts Committee on Public Safety. Meanwhile, having maintained his connection with the Army as a member of the Medical Officers Reserve, he had been advanced from major to colonel. On July 18, 1942, he was ordered to active duty and immediately became chief surgical consultant, European Theater of Operations. To comment on his accomplishments during that time is unnecessary. All who served under him know what an enormous influence for better surgery he was and how remarkably he improved and aided in the organization of our extremely efficient Medical Service. He was one of the few medical officers who entered for the emergency who was recognized by promotion to the rank of brigadier general.

During his tour of duty in Europe, he visited the medical services in all unoccupied territories and had the great honor of visiting with the Russian Medical Corps. His Army work accomplished, he returned to his old position as Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief of the Peter Bent Brigham Hospital.

\*This and the succeeding paper comprise the addresses delivered at the presentation of the Henry Jacob Bigelow Gold Medal at a meeting of the Boston Surgical Society, Boston, June 2, 1947. The recipient of the medal, Dr. Elliott C. Cutler, died on August 16, 1947.

†President, Boston Surgical Society

In 1947 he was appointed acting assistant medical director for the Professional Services Division of the Veterans Administration. His work in this field has been superb. A comparison of the veterans hospitals of today with those of yesterday offers a real idea of the value of this contribution.

He has in his life, as one look at his record shows, done extremely important work in surgery, in research and in teaching. He has found time to belong to a great many civic organizations and may be considered a great public servant. He has been made a member of nearly all surgical associations and clubs and has been honored and decorated not only by his own government but also by those

of England, France and Norway. There are few physicians in our time who have done more work, who have taught more delightfully, who have inspired more young men and who—in spite of a full and busy life—have given more time and work to civic pursuits. And few have given more to their country.

Many are the reasons for presenting the Bigelow Medal to Dr. Cutler, the greatest being that he is the embodiment of the many things that most young men aspire to be.

It is an honor to the members of the Boston Surgical Society to present this medal to you, Dr. Cutler.

## THE EDUCATION OF THE SURGEON

ELLIOTT C. CUTLER, M.D., Sc.D. (hon.)\*

BOSTON

I AM highly sensible of the great honor done me tonight by the Boston Surgical Society through this presentation of the Henry Jacob Bigelow Gold Medal. As one who has attended the presentation of this honor to all previous recipients—ten during the past twenty-five years—and who knows the unusual gifts and attributes of my predecessors, I am overcome with my own inadequacies. Indeed I have done little more in surgery than many of my own age group in Boston. At the same time, I deeply regret that because of difficulties beyond my control, I have been prevented from giving the time and energy to this oration that the occasion richly justifies. Certainly, no greater honor can come to an American surgeon.

I hope that I shall be forgiven if, in introducing my topic, I utilize in part personal experiences that perhaps explain my way of thinking. In fact, the story of my "breaks" with traditional surgical education in Boston is a reason for the very use of my topic, and may have played a larger part in this generous presentation of tonight than is imagined. When I was a medical student, the fourth-year courses were entirely elective, and although a few brave spirits had hidden themselves away in some special laboratory for as long as six months of this last year and, perhaps, in one or two instances for a whole year, this was not considered the proper way to achieve entrance to the better hospital services. During my third year in the medical school, however, I made up my mind that I was to see plenty of surgery in my lifetime and, therefore, should not devote a valuable year to clinical surgery, particularly under the hodgepodge monthly-assignment system then in vogue. Dr.

Harvey Cushing, who had already started to guide my errant steps, urged me to put in a year with Dr. Walter Cannon, and although all medical students of my age admired and loved Walter Cannon, as all men did who came to know him throughout his long and productive life, I had come under the influence of Dr. Councilman, professor of pathology at Harvard Medical School, and elected to spend my fourth year with Dr. Frank B. Mallory in his laboratory at the Boston City Hospital. I suspected that many of my teachers, especially the practicing surgeons of Boston, thought that this was a rather foolish enterprise. Yet, as I look back on that precious year, it probably did more for me as a budding young medico than any other year in my lifetime, for with Dr. Mallory I learned the value of precise work and the importance of making and recording correct observations, and I learned to enter the domain of books, for there is time in the life of the laboratory worker to read and study and thus to become aware of the immense amount of knowledge available to the profession. And, finally, I learned some pathology. This is one of the cornerstones of surgery, for if the surgeon cannot tell, let us say, inflammation from tumor in the midst of a perilous abdominal procedure, he can never become a really competent surgeon and is nothing more than a handicraftsman. Moreover, it was this year with Dr. Mallory that led me to spend the next nine months in Krehl's laboratory in Heidelberg, working on a problem that involved pathological disciplines as well as surgery and medicine.

I broke with tradition in this city when I selected the new Peter Bent Brigham for my surgical training. This for me was merely the fulfillment of an ambition to work with Dr. Cushing, who had made,

\*Moseley Professor of Surgery, Harvard Medical School, surgeon-in-chief, Peter Bent Brigham Hospital.

early in my medical-school days, an immense personal impression on me. I had already determined to go to Johns Hopkins to work with him after graduation from medical school, only to find that he was coming to Boston. This prevented a change of environment that I had hoped might broaden my medical horizon. After an internship at the Brigham Hospital and a sojourn in a military hospital in Paris, I was most grateful to the Massachusetts General Hospital Staff for accepting me, in 1915, as resident surgeon. There I greatly benefited from the example and opportunity presented to me by the senior members of the West Surgical Service, especially Drs. George W. W. Brewster and C. Allen Porter. This interchange of house staff between the two hospitals was the innovation of a happy custom.

After a year at the Massachusetts General Hospital I again broke with tradition, incurring this time the disapproval of my beloved chief and mentor, Dr. Cushing, by moving to the Rockefeller Institute and studying immunity under Dr. Simon Flexner. I had been offered the privilege of taking over the Hunterian Laboratory at Johns Hopkins by Dr. Halsted, but I came to believe that if I did that I should still be in the environment of clinical colleagues, because so many of the young surgeons there were already friends of mine, and I wished to keep away from the clinic as much as possible so that I could benefit from the stern discipline of a meticulous laboratory worker. I well remember the alarm and even disapproval in the minds of several older surgeons in Boston, who were friends of my family and to whom I had often gone for advice, when I told them I was to study immunity. A leading surgeon of that day asked for information concerning the topic and told me he had never had cause to use such information in his practice!

Then followed World War I and its tremendous experience both in traumatic surgery and in the handling of multitudes of patients. In that war I was privileged to be chief of the professional services in an evacuation hospital and although a lowly captain, taking over from a full colonel in the regular Army, I managed to weather the storm and benefited greatly from the administrative experience of trying to keep a large hospital going all the time, up the line, in the mud, without supplies or much assistance. To be sure, I pilfered liberally from the battlefields, but I rarely complained to headquarters, perhaps because I dared not confront high-ranking people, which left me in the good graces of the chief surgeon of the Theater.

After the war there were further years of training at the Brigham Hospital. Nine years after I had graduated from medical school, I quitted the post of resident surgeon at the Brigham Hospital, becoming a junior member of the staff and spending most of my time in the Surgical Laboratory, studying

cardiac surgery. Seen in retrospect, such a bringing up separated me and my ambitions from most of my contemporary colleagues. That I did not know when and where I should settle into an academic life did not seem to bother me at the time, for I was busy and happy in the laboratory. Meanwhile, the Rockefeller full-time plan had just begun, and although it had followed the voluntary full-time arrangement set up by Drs. Christian and Cushing at the Brigham Hospital, it had attracted many followers. I recall long discussions with Dr. Francis W. Peabody and remember that we both believed that there might be certain drawbacks to the Rockefeller system in that the teachers and the men to come under the plan would be robbed of the opportunity to care for their own patients—an important matter, which they were supposed to be able to teach to their students. On this basis I am sure, both Dr. Peabody and I, at that time and later, turned down the Rockefeller full-time system.

The next year, 1923, was a hectic one for me because two medical schools offered me professorships and another discussed the matter with Dr. Cushing and myself, but having taken a look at the candidate, never reappeared. Finally, in 1924, the School of Medicine of Western Reserve University, in Cleveland, made me an offer. The opportunity seemed excellent, and the die was cast. That school, moreover, accepted the so-called "Harvard full-time plan," which was what I desired. No previous clinician had had his office within the walls of the Lakeside Hospital, and when I took over some of the private ward rooms for offices for myself and my young colleagues, it created quite a disturbance. Moreover, I had demanded a good laboratory, and that led the school to more of a financial outlay than perhaps it had anticipated.

The difficulties of transplanting one's self and one's family to a strange city were finally surmounted, although it took several years for the local profession and the populace to realize that the young professor was fit to conduct surgical procedures on men as well as on dogs. It had been rumored about Cleveland before I came that I was an excellent laboratory investigator and knew about the surgery of animals, but had had little experience with man. Even this difficulty, however, had its beneficial side, for it forced me to stick to my laboratory and my wards and to teaching, and to leave the practice to my older colleagues, who were thus made happy and who became eventually my warmest friends and supporters.

Thus, by my early preferences, my training and my first experiences in a clinic of my own, I was directed toward a truly academic life, and tonight I shall speak of the training of the surgeon. Whether or not I have profited by consistently following a course that has for so long been the subject of my thoughts and ambitions, you shall be the judges.

The education of the surgeon really does not begin until he leaves medical school. Yet teachers in graduate schools must consider the early education of the student material handed on to them. It is always to be regretted that in the primary schools little thought is given to the scientific method. All early education is either logic (mathematics) or memory, and memory is the simplest of intellectual functions. And it has seemed a pity that the student's powers of observation and the synthesis of ideas should not have been given some practice. Moreover, postgraduate educators must rely on the medical school for the proper teaching of the medical laboratory disciplines. The surgeons have long decried the diminishing emphasis on anatomy, and now they must worry about the amount of pathology and bacteriology given to their students. Are medical students aware that every operation is an experiment in bacteriology, and are they well grounded in physiology? In my opinion, the medical-school education should be sufficiently broad and sound to allow the student to enter at once into his training as a surgeon. I decry the value of the rotating internship year, now so widely proposed throughout this country, in the education of the surgeon. To my mind, it is merely adding another year to a young man's period of study when he should be getting on with his career. I have long held that the fourth year at the Harvard Medical School is as good as any rotating internship in the country and that students are ready to begin their studies as medical or surgical workers in the broad sense from the moment they leave school. Other Grade A schools are in a similar position. Life is short enough without forcing on the young doctor this additional year, which he cannot well afford, he must some day be prepared to support himself and a family. Moreover, when the student makes up his mind whether he is going into medicine or surgery,—and he can put off a narrower specialty in either of these fields until a later date,—he is wise if he studies the whole hospital plan of the institution where he is to be an intern and is sure that he can acquire there his complete surgical education. This means at least five and usually six years. By that time, he should be fully qualified in the technical art of surgery, should have had enough experience to be proficient in the handicraft side of surgery and, by having been given responsibility as a resident surgeon, should have developed confidence in the practice of his art.

I also wish to emphasize the importance of such an education's being acquired under a single master. Young surgeons who change hospitals frequently never stay long enough to evoke the final interest of the chief surgeon, and since this education is essentially the apprenticeship method, much that is best is lost. It should be pointed out that the education of the physician and that of the surgeon

differ essentially in that although many may profit from the medical examination of a patient with a cardiac murmur or some unusual medical sign, only the person who himself conducts the operative procedure can fully benefit from that experience. This handicraft aspect of surgery is something that must be learned, and it must be learned under the most careful tutelage. The young surgeon finally reaches the point where he must be given individual surgical responsibility and the opportunity to operate independently. Only by such practice can he acquire confidence, which is essential to his final development.

The internship should occupy about eighteen months and should be a graduated system in which the beginner progresses from little responsibility to greater responsibility. Thus, he can begin as a worker in the clinical laboratory and finally progress to senior intern on the ward, with perhaps the most junior intern under him, where he is early given the responsibility as a teacher that is a healthy experience. Those who teach are apt to be most thorough, for to teach one must know the subject, which cannot be glossed over before students in the hope that they will assimilate something that has not been told to them. Moreover, this internship year should give him experience not only in general surgery but also in most of the surgical specialties, and the young surgeon must therefore go to a hospital where all aspects of surgery are covered and preferably where they are grouped under the chief surgeon and go into a common internship experience. This year is also rendered more profitable if toward the end of the tour of duty he works in an outpatient department and has the opportunity to care for ambulatory patients who are his direct charge and responsibility and who come back for observation or further study as he directs. While working in the outpatient department he should be under the careful guidance of staff members as well as the residents on his own service, for here he will achieve experience in conducting himself as in his own office practice in the years shortly ahead of him. It is proper to remark that the appointment of an intern is the most important responsibility of the staff of a hospital. If the material chosen is good, there will be a happy house staff and an excellent *esprit de corps*. Moreover, if the interns are competent, the better ones chosen to be assistant residents later on will be of superior caliber, and as the weeding-out process continues, excellence always remains. To draw good interns means close association with medical students, working hard over clinics and all student engagements, and having it generally known that at such and such a hospital the members of the house staff are well treated, carefully guided and always helped when in need. If a hospital is drawing good interns, it usually means that the staff

has been working hard with medical-school responsibilities

After the internship he should move on to an assistant resident's post, which should occupy about two years and cover periods of four months, at least, in genitourinary surgery, neurologic surgery, orthopedic surgery and gynecology, as well as a major part of his time on the general surgical wards. I hope that while in his major period on the general surgical wards he would have some experience with thoracic surgery, plastic surgery and other less well defined or even narrower surgical specialties. This period as assistant resident should bring the embryo surgeon into close contact with the entire domain of surgical endeavor. It should disclose to him the limitations as well as the possibilities of surgery as a therapeutic agent. His proficiency in the handicraft aspect — what I have called the art of surgery — will greatly increase, and by the end of the period he should be able to perform with safety most of the standard surgical procedures. Such a system for an assistant residency in surgery is again, as with the internship, better if the incumbents begin at intervals of three or four months and then move on into the successive stages of their training as new incumbents arrive. Such a rotation and succession gives to the hospital one man about to complete his service who should be capable enough to substitute for the resident surgeon when he is off duty and thus leave the hospital always well protected. In fact, it is wise to call attention to the fact that any system providing better care of the patients is always the better system — for the pupils, as well as for the patients. Moreover, such a progressive system leaves it incumbent on the senior members of the house staff to teach the newcomers to the service. Here, again, an advantage is achieved both for the patients and for the men in training. A sense of responsibility is developed by this teaching opportunity, and willy-nilly the pupils grow in stature, ability and reliability. After twenty-three years as a professor of surgery, I am convinced that nothing is better for the pupil, as well as his ogre-eyed master, than the steady development of this sense of responsibility. Once it is inculcated in the intern and then polished in the assistant resident it blooms with great vigor and is the major magic in a satisfactory *esprit de corps*.

Having completed his assistant residency, the young surgeon has had three and a half years of sound training in a school for surgery using a common and standardized technic, which is better than if he had served his internship in one hospital, using one technical method, and then moved for his assistant residency to a second hospital where quite a different technic is practiced. Changes of hospital tend to confuse the budding surgeon. He has little knowledge by which to judge which is the better technic and thus may find himself later on practicing a less desirable technic or one that,

because he was not deeply enough trained, he does not practice well, with the result that he finds himself a second-rate technician rather than a first-class one. Nevertheless, when the surgeon has put in his three and a half years, the next step should be a year in a laboratory.

This laboratory year is the crucial turning point in the career of the young surgeon because, for the first time, he really begins to think independently. Here, medical training has another aspect that differs from surgical training. The surgical interns and assistant residents are apt to be so busy with important, often life-saving, measures that they do more or less what they are told to do and rarely have the time to sit down and think out exactly why they should do a thing or read up on a topic to see that it is proper. The physician, after his morning rounds, does not have to go through three to five grueling hours of physical labor in the operating room applying his therapy, for his therapy has long since been written in the order book. Therefore, with plenty of time to discuss matters, he can sit down and read up on subjects that have been brought up and that he questions. The surgeon is too busy for such relaxation and education, or perhaps he is physically too tired and cannot force himself to hours of study when that is what he needs most. I have long regarded a year in the laboratory as the period that rapidly differentiates growing young surgeons and in which one can soon pick the good, the bad, the indifferent and the exceptional men. The young surgeon, coming from a busy life in which each moment has been dictated by necessity, is often downcast and depressed when put in a laboratory by himself, particularly so if he is left alone and not helped. He feels lost, as if there were nothing to do. But this is the vital point in his career. He must be left alone because he must learn to think for himself. He has been given a problem but does not seem to know how to go about it. It is unwise for even the most generous teacher to help his pupil at that time. Once the young man has learned to think out a problem, stand on his own feet and go to the library and read books, he bursts into his chief's office full of new ideas, and the world is a different place for him. From then on his chief can work with him as much as he wishes in the laboratory, and the two will have great fun together. But the teacher must not do this too early or before the pupil has learned to think and study, lest he injure the pupil's career and his ambitions. It is remarkable how rapidly the young man develops at that time. And at the end of a year that, ten months previously, had seemed so hopeless, he often begs for another year in the laboratory, a request that often cannot be granted because he is needed to become the resident surgeon and to carry on the full responsibilities of running the hospital.

Thus, at the end of four and a half years the surgeon is well trained. He has acquired the technic and the handicraft of surgery, and he has learned how to think. The momentous changes may never be known to anyone but his chief, but the latter will recognize that the change has occurred and that another safe surgeon is ready to carry the torch.

I have spoken as if the product was complete and finished. That is not fully true, although the young surgeon will do well anywhere with the training he has obtained. But this man can be better prepared by being given greater experience and responsibility. This is especially true if he anticipates leading the life of the teacher and investigator in surgery. I pointed out above that only one person receives full benefit from an operative procedure, and that is the surgeon conducting the operation. As an intern, a few simple surgical procedures can be given to the young surgeon under guidance, while he is assistant resident more procedures should be permitted him, and he can safely conduct the simpler ones without assistance but not the greater procedures, which therefore should not be completely relegated to the young surgeon. It is true that the assistant resident surgeon at the end of three and a half years in a good clinic should be so well grounded in the principles of surgery that he can conduct any procedure well. Indeed, in the recent war I watched with delight surgeons only three or four years out of medical school conducting the most complicated thoracoabdominal procedures with complete assurance and great technical polish. A final year in the hospital as resident surgeon will give to the assistant resident surgeon all this assurance and polish and will leave him time to begin to put together his first medical contributions. All teachers should wish to propagate their kind and to leave pupils who can occupy chairs of surgery with distinction. The exceptional man will therefore be chosen by his chief to be the resident surgeon at the hospital. This person represents the attrition of the original young graduates who began together as interns and who saw their first losses when the assistant-resident posts were granted.

The resident surgeon is the head of the house staff. He directs the work of the interns and assistant residents and continuously instructs them, he admits and discharges surgical cases, keeps a watchful eye on the outpatient department and may even advise the laboratory fellow, for all who are not staff members fall under his authority. He is held personally responsible by his chief for the care of all seriously ill patients and must report immediately on all accidents or untoward occurrences on his service. With the visiting staff, he sets the schedule of operations and picks those that he wishes to do. At night he uses his judgment whether to call in a staff member or perform the necessary operation himself. And all the time he is responsible for organizing the undergraduate teaching and for informing staff members of their engagements with students. This is a wide scope of responsibilities, but on its successful performance depends the smooth functioning of the service. After a year or two of such responsibilities, the resident surgeon has absorbed all that a position on the house staff can give him. He may go out to settle in practice or to work up on a senior staff elsewhere, or he may be chosen by his chief to join the senior staff in the hospital where his training began. This resident surgeon represents the finished product in the education of the surgeon. He has been given exceptional experience and great advantages. On his shoulders rests the responsibility for educating another generation of surgeons.

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My story is incomplete, but in handing it on to others I can only hope that they will achieve the happiness that has been mine in the devotion and success of pupils. No way of life can bring greater satisfaction than that which comes to those who enjoy teaching and have the rare privilege of being kept young by disciples. In closing my part of this ceremony I wish to thank the members of the Boston Surgical Society for the great honor that they have this evening given to me.

## WEIL'S DISEASE\*

## A Report of Twenty-Three Cases

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ALTHOUGH Weil's disease is frequently mentioned in various classifications of the causes of jaundice, it has attracted little attention as a condition that can simulate an acute surgical condition of the abdomen. This is not at all surprising because the disease is generally considered to be quite rare in this country. In fact, state and city health departments have only recently become equipped to undertake the proper diagnostic laboratory procedures.

We became interested in this problem during a review of cases of jaundice at Charity Hospital of Louisiana in New Orleans, in which it was found that operations had been performed on 2 patients who subsequently proved to be suffering from Weil's disease. Further investigation revealed that in the six-year period from June, 1939, to June, 1945, a total of 23 cases of Weil's disease were diagnosed and treated correctly. In 1943, Bruno, Wilen and Snively<sup>1</sup> reported 15 of these cases. Such a large group of cases affords a unique opportunity for the study of this specific infection.

The usual problem in the jaundiced patient is to decide whether the jaundice is obstructive, hemolytic or hepatogenous in origin, and whether operation is indicated. The difficulty in the differentiation of these types of jaundice has been considerably reduced by the newer concepts of liver physiology and bile-pigment metabolism. Steigmann, Popper and Meyer<sup>2</sup> have shown that the correct diagnosis can be made in 95 per cent of patients by careful clinical observation, prolonged study of the urinary excretion of bile pigments and judicious use of liver-function tests.

A case of Weil's disease, however, may turn out to be a diagnostic problem during two separate and well defined stages in the course of the illness. In the incipient or so-called "septicemic phase," the clinical picture can mimic an acute surgical condition of the abdomen so closely that operative intervention is deemed essential. On the other hand, once the second, or icteric, phase of the illness has developed, it must be recognized that the jaundice is not obstructive in character and that surgery is contraindicated. Diagnosis during the second stage of the disease is relatively easy because there is usually sufficient time to study the patient and to determine the results of the various laboratory tests required to establish the true nature of the illness.

It is evident, therefore, that the greatest difficulty in the correct diagnosis is in the prejaundice phase of Weil's disease, when the symptomatology is variable and misleading. This is borne out by the fact that the only patients in the series who were subjected to surgery were operated on during the early stage of the disease before jaundice was evident. Surgical consultations were requested for 5 additional patients, but in each case jaundice was present and additional laboratory procedures were recommended to establish the diagnosis.

Once these facts became apparent, it was considered worth while to review in detail the 2 operative cases and to discuss the clinical aspects of the other 21 cases to stimulate interest in this disease.

**CASE 1.** E. J. F. (T-40-43067), a 38-year-old housewife, was admitted to the hospital on April 20, 1941, with the complaints of colicky pain in the upper abdomen, nausea and vomiting, a high temperature and backache. These symptoms had begun about 2 days previously, and during the interval severe epistaxis had occurred.

Physical examination revealed a well developed well nourished woman who appeared acutely ill. No abnormal findings were noted on examination of the heart and lungs. Palpation of the abdomen revealed tenderness in the right upper quadrant. The liver edge was thought to be barely palpable, and voluntary guarding of the abdominal muscles was noted.

The temperature was 104°F, the pulse 116, and the respirations 24. The blood pressure was 128/68.

Examination of the blood disclosed a red-cell count of 4,500,000, with a hemoglobin of 70 per cent, and a white-cell count of 19,600 with 86 per cent neutrophils, 12 per cent lymphocytes and 2 per cent monocytes. The urine had a specific gravity of 1.008 and gave a + test for albumin but contained no sugar or bile. Microscopical examination of the sediment revealed no cells or casts.

A provisional diagnosis of acute cholecystitis was made. The patient was taken to the operating room on the day of admission, and cholecystectomy was performed. At operation the gall bladder was slightly distended but showed no evidence of inflammation. The liver was moderately enlarged.

During the 1st week after operation the high temperature continued, and the patient suddenly developed marked jaundice. On May 3 the icteric index was 36, and the blood urea nitrogen 36 mg per 100 cc. Agglutination for *Leptospira interrogans* reported by the United States Public Health Service was 1:3000 on May 2 and 1:30,000 on May 6. Supportive therapy with 5 per cent dextrose infusions and blood transfusions was promptly instituted. During the third week of illness the jaundice diminished. An uneventful recovery followed and the patient was discharged on May 20.

The history and physical examination in this case justified the diagnosis of acute cholecystitis. There were practically no early indications of the true nature of the disease except the backache and the possibility that the nosebleed was a manifestation of the hemorrhagic tendency often present in Weil's disease. The temperature of 104°F was higher

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than is ordinarily expected in the usual case of uncomplicated early cholecystitis. When jaundice developed, the possibility of a common-duct stone overlooked at operation was considered. This was ruled out rather promptly, however, by various laboratory tests.

CASE 2 E G (I-42-60881), a Negro, was admitted to the hospital on August 30, 1942, with a history of an illness of 3 days' duration. Malaise and anorexia were the primary symptoms, but the patient soon developed pain in the right upper and lower quadrants of the abdomen. Nausea and vomiting occurred frequently during that time, and a cough also developed.

Physical examination disclosed a patient who appeared acutely ill. The heart and lungs were clear to percussion and auscultation. The right side of the abdomen was tender, especially in the right lower quadrant. No rebound tenderness could be elicited, however, and only voluntary rigidity was present. The liver was described as being palpable.

The temperature was 102°F, the pulse 100, and the respirations 25. The blood pressure was 105/60.

Examination of the blood disclosed a red-cell count of 4,300,000, with a hemoglobin of 11.5 gm., and a white-cell count of 12,500, the differential count showing a shift to the left. The urine had a specific gravity of 1.012 and gave a + test for albumin, with no sugar or bile and a trace of urobilinogen. The sediment contained occasional red cells and white cells.

A tentative diagnosis of acute appendicitis was made, and an emergency appendectomy performed. The appendix appeared normal at operation but was removed. Postoperatively, the patient continued to have fever, and on September 3 he became jaundiced. The icteric index rose to 51, and the blood urea nitrogen was reported as 45 mg. per 100 cc. Bile was present in the urine, and occasional granular casts were seen in the sediment on microscopical examination. Agglutinations for *L. icterohaemorrhagiae* were reported as 1/30 but rose to 1/3000 5 days later. Conjunctival hemorrhages appeared, and the patient's general condition grew worse for a few days. The patient was treated symptomatically with blood transfusions and dextrose infusions. Subsequently, the fever subsided, the jaundice cleared, and the patient was able to leave the hospital on September 11.

This patient was examined in routine fashion, and the emergency appendectomy was performed on the basis of the pain in the right side and the elevated white-cell count. There were several factors, however, that might have aroused the suspicions of the examiners. The cough at the onset of the illness, the absence of more signs of peritoneal irritation in the presence of an apparent acute appendicitis of three days' duration and the presence of albumin and cells in the urine were suggestive of a condition other than appendicitis. The difficulty in diagnosis was caused by the fact that jaundice did not appear early, which is true of most cases of Weil's disease.

Since the disease can readily be mistaken for an acute abdominal condition requiring surgery, the clinical aspects should be kept in mind so that it may be suspected early and prompt action taken to establish the diagnosis.

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In 1886 Weil<sup>2</sup> first published his classic description of a specific infectious disease that has since been known as Weil's disease. In his report of 4 cases he was able to describe the condition in detail and to differentiate it from other types of acute

jaundice. The illness of his patients was characterized by severe chills, marked prostration, jaundice associated with hepatolienal enlargement, a hemorrhagic tendency and signs of renal failure.

Weil's observations stimulated others to look for this disease, resulting in a marked increase in the number of cases reported in foreign countries. It was not until 1922, however, that Wadsworth<sup>4</sup> published the first account of a proved case of Weil's disease in the United States. From 1922 to 1941 Ashe, Pratt-Thomas and Kumpe<sup>5</sup> were able to collect a total of only 67 reported cases in this country.

### Epidemiology

In 1916 Inada<sup>6</sup> found that the etiologic agent was a spirochete that was later classified and named *L. icterohaemorrhagiae* by Noguchi.<sup>7</sup> The usual vector is the adult gray rat, and the rat population serves as a main reservoir for the spirochetes. The majority of cases occur as a result of contamination of the skin by the urinary excretion of infected rats. The organisms can live in a warm damp environment for days and may produce the disease in man by penetration through the nasal mucous membrane,<sup>8</sup> the conjunctivas<sup>9</sup> or abrasions of the skin.<sup>10</sup> The disease is an occupational hazard to miners, sewer workers, fish cleaners and tunnel diggers. Rat elimination is the logical method for the control of the disease. Individual protection by avoidance of water or food likely to be contaminated by the excreta of rats should be practiced. The control problem is understandably difficult, and in New York Weil's disease is now recognized as a compensable disease in fish handlers.

### Incidence

Weil's disease has been reported to be rare in children. The youngest patient in this series was thirteen years of age. Twenty of the patients were males, and 4 were females—a ratio of 5/1, as compared to that of 9/1 generally reported in this country. Davidson<sup>11</sup> has demonstrated that the difference in incidence between the sexes is purely occupational.

The reported seasonal incidence during the summer months is adequately illustrated in this series. Most of the cases occurred between April and October, 50 per cent of patients entering the hospital during August and September.

### Clinical Features

The incubation period in these cases could not be determined, although it has been reported to average about ten days, with a range of four to nineteen days. The clinical course of the illness may be divided arbitrarily into three stages.

The first or septicemic stage usually lasts from two to five days and is characterized by the presence of spirochetes in the blood stream. The patient complains of an acute onset of nausea and vomiting,

myalgia, prostration, fever and chills. The bradycardia occasionally described was not found in any of the cases reviewed, the pulse rate varying from 110 to 150 per minute. The skin is hot and dry, and petechial hemorrhages may be found anywhere in the body. Abdominal pain is frequently present, although the abdomen is usually found to be soft and scaphoid. Tenderness may be elicited in the right upper quadrant, but there is no evidence of peritoneal irritation. Careful palpation reveals that the tenderness is frequently located in the abdominal wall itself and is probably caused by pathologic changes in the muscles.

The second or toxic stage is ushered in with the onset of jaundice. All but 1 patient in this series became icteric, although world statistics indicate that only half the patients with Weil's disease develop jaundice. Patients without jaundice do not have a second stage but proceed directly into the third or convalescent period.

Jaundice develops most frequently between the fourth and eighth days and is rarely accompanied by pruritus. Evidence of renal damage is also found at about that time. The patient appears extremely ill and may become stuporous, with occasional progression into coma or delirium. The temperature drops from the level of 104 to 106°F seen in the first stages to 100°F or even to normal. Signs of bronchopneumonia, with blood-streaked sputum, may be found. The liver becomes enlarged and tender. In 4 cases of this series the spleen was enlarged, although it has been stated by Ashe, Pratt-Thomas and Kumpe<sup>6</sup> that the spleen is usually not palpable.

The convalescent stage is reached after the second week in patients who do not succumb. Kidney and liver function improve slowly after that time, the jaundice recedes, and the fever, which may have persisted into the second stage, subsides. During that period the patient complains only of weakness. Convalescence is complete as a rule in about four to six weeks.

All the patients with Weil's disease whose cases are reviewed were acutely ill on admission to the hospital and had one or more of the manifestations presented in Table 1. The onset of the disease was sudden in 18 cases, and 12 patients remembered the exact hour at which they had become ill.

The laboratory data found in this group of patients were in agreement with those described in the literature. In most cases the white-cell count ranged between 9500 and 24,000. One patient was found to have a leukemic level of 35,000, with a marked shift to the left. The urinary findings in these cases reflected the kidney damage that is present to some degree in all cases of Weil's disease. Albumin, red cells, a lowered specific gravity and a lowered phenolsulfonephthalein excretion were found in practically all cases. The blood urea nitrogen was above 100 mg per 100 cc in 10 patients, and in 1 it was 150 mg. The icteric index rose to

300 in 1 case, the average, however, ranged around 76. Cephalin-flocculation, hippuric acid and galactose-tolerance tests, when done, showed evidence of liver damage.

The agglutination titer for *L. icterohaemorrhagiae* was 1:300 or above in the 23 cases reviewed. Tests below 1:300 were not considered diagnostic of Weil's disease. Rising titers occurred in 17 patients and were of value in establishing the diagnosis when there was doubt regarding the etiology of the disease.

Spirochetes were seen on dark-field preparation in only 1 case. The neutral urine or the blood of 4

TABLE 1 Symptoms and Signs in Weil's Disease

SYMPTOMS AND SIGNS	NO. OF CASES
Fever	23
Headache	17
Muscular aches	17
Jaundice	22
Abdominal pain	15
Vomiting	19
Chills	17
Cough	8
Stiff neck	1
Irrationality	3
Clay-colored stools	3
Palpable liver	18
Palpable spleen	4
Abdominal tenderness	18
Hemorrhagic tendencies:	
Petechiae	3
Conjunctival hemorrhage	6
Gingival hemorrhage	3
Epistaxis	2

patients when inoculated into guinea pigs produced findings characteristic of Weil's disease.

### Diagnosis

Various provisional diagnoses were made either on admission or after a brief clinical survey before the diagnosis could be confirmed. Weil's disease was considered the most reasonable possibility in 8 cases, acute catarrhal jaundice in 8 cases, acute cholecystitis in 3 cases, bronchopneumonia in 2 cases, appendicitis in 1 case, and typhoid fever in 1 case. A high index of suspicion is evident from the fact that fully 33 per cent of patients were admitted with a tentative diagnosis of Weil's disease, requiring only confirmation by laboratory procedures.

A definitive diagnosis can be made in the first week of the disease by examination of the blood under dark-field illumination or intraperitoneal injection of 5 cc. of the patient's blood into a young, preferably pure-white, guinea pig weighing 175 gm or less. In the presence of the disease the young pigs become jaundiced and die in from ten to fourteen days. The spirochetes can then be found in the peritoneal fluid of the animal and in various organs.

On dark-field examination the organism appears as an actively motile spirochete from 8 to 15 microns in length and approximately 0.5 micron in width. It is tightly coiled and usually appears as a series

of brightly refractile spots alternately interspersed with nonrefractile areas of the same size. *L. ictero-haemorrhagiae* differs from *Treponema pallidum* in that it is more tightly coiled and has a sharp hook at one or both ends, which gives the organism an "S" or "C" shape. Careful study may be necessary to differentiate it from the numerous fibrin particles, which exhibit Brownian movement. Incubation at 27°C frequently increases the number of organisms in the specimen and aids in their demonstration. Examination of the urine is often of value during the second week, when the organisms are frequently present. Injection of the centrifuged sediment from 60 to 80 cc of fresh neutral urine diluted with 5 to 10 cc of physiologic saline solution into the peritoneum of a young guinea pig usually causes the death of the animal at the end of two weeks. Spirochetes can then be seen in the various organs by means of the Levaditi or Giemsa stain.

At about the end of the second week of the illness, antibodies appear in the patient's serum and agglutination tests may be performed. These tests are ordinarily of no value before the ninth day. Strongly false-positive reactions do not occur, and a negative agglutination test after the thirteenth day of illness rules out Weil's disease. High titers may persist for long periods.

### Pathology

Post-mortem examination was performed on 2 patients in this series, and pathologic changes were noted primarily in the lungs, kidneys and liver. The lungs showed patchy areas of bronchopneumonia. The kidneys revealed interstitial infiltrations of round cells. The glomeruli were not remarkable but showed some enlargement of the capsular spaces. The tubules were dilated and filled with small amounts of amorphous pink-staining material. The tubular epithelium was swollen and granular. In 1 case Levaditi stains revealed numerous spirochetes within the tubules and in the surrounding stroma. The liver on microscopical examination showed considerable disorganization in the arrangement of the liver cells, which, instead of appearing in continuous cords, occurred in groups of two or three cells. Moderate vacuolization and swelling of the cells were noted. There was no evidence of intrahepatic block. Levaditi stains did not disclose spirochetes in either case.

These findings are in agreement with those described in the literature.<sup>5, 8, 12</sup> Lesions in capillaries and skeletal muscles have been reported frequently. Capillary damage is manifested by numerous small hemorrhages, which can be found almost anywhere in the body, or by severe hemorrhage from any epithelial lined surface that can give rise to symptoms such as melena, hematuria, epistaxis and hemoptysis.

The changes in the muscles have been described as follows by Jeghers et al.<sup>8</sup>

There is vacuolization, swelling, loss of cross-striations, hyalinization, infiltration with histiocytes, polymorphonuclear leukocytes and plasma cells, breaking up the substance of the fibers into larger, round lumps of hyaline material, and reabsorption and proliferation of the nuclei of the sarcolemma.

The mechanism of the jaundice in Weil's disease has not been established. Ashe and his associates<sup>1</sup> state that the jaundice is probably due in large part to a true hepatitis. Increased hemolysis or intrahepatic obstruction has also been described by others as a factor in the production of jaundice in Weil's disease.<sup>13</sup>

### Treatment

Arsenical drugs have no effect on the spirochetes and are dangerous in the presence of liver and kidney damage. Antimony compounds and sulfonamide drugs are also of no benefit.

Success has been reported in a few cases by treatment with sodium bismuth tartrate.

The therapy of choice at present is the use of penicillin in large dosage and of immune serum. The latter has been used in foreign countries with considerable success but has only recently become available in this country. Up to the present, transfusions of convalescent plasma or blood have been used. Four of the cases reviewed in this series were treated by the latter method and showed a marked response. The rest of the patients were treated by general supportive measures. Penicillin was not available for use in any case.

### Mortality

There were 2 fatal cases in this group of 23 patients, a mortality of 8.7 per cent. Ashe, Pratt-Thomas and Kump<sup>6</sup> found that the mortality in this country averaged 30 per cent. It is entirely possible that a number of patients in Charity Hospital of Louisiana died in the early stages of the disease before the diagnosis had been suspected, which may account for the relatively low mortality figure in this group.

### SUMMARY

Two cases of early Weil's disease subjected to surgical exploration are reviewed in detail.

The clinical features of 21 additional cases are discussed.

Acute surgical abdominal disease and extrahepatic biliary obstruction can both be simulated by Weil's disease, which must therefore be considered in the differential diagnosis.

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## CARCINOMA OF THE BREAST

### End-Results Massachusetts General Hospital 1933-1935

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THE present communication is the eighth in a series of reports from the Massachusetts General Hospital dealing with the results following operation for carcinoma of the breast.<sup>1-7</sup> There were 382 cases of carcinoma of the breast during the three-year period, 1933-1935, of which 328 were primary cases and 54 had received earlier treatment elsewhere. Of the former, 92 were inoperable when first seen, and 236 (72 per cent) were submitted to radical operation. Two cases that were untraced are regarded as failures, and 14 cases in which the patients died of intercurrent disease within five years are considered inconclusive. There were 5 postoperative deaths (2 per cent). Although historical data are incomplete, it seems probable that poor initial medical advice accounted for an advanced stage of the disease and consequent failure of cure in 19 patients. In 20 patients the original description of the lesion, with extensive matted axillary involvement, suggested that the operation was ill advised. These patients all succumbed to prompt recurrence, in 17 cases within a year of operation, although all received postoperative x-ray therapy.

In the present series, 40 per cent of patients reported for treatment within two months of the onset of the disease, whereas in 35 per cent the delay was more than six months. In the previous series of cases reported, only 31 per cent delayed over six months after onset. It should also be noted that the operability rate was 80 per cent in the previous series, compared to 72 per cent in the present group. Thus, it cannot be shown that propaganda has succeeded in shortening the time between the first symptom and operation, nor has

it caused patients to report in a stage more favorable for cure. On the other hand, the disease was limited to the breast without axillary metastases in 40 per cent of cases, in contrast to 37 per cent in the previous group. This fact, in conjunction with the lessened operability percentage, suggests that criteria of operability have been sharpened. There is still room for improvement in this respect, however, as shown by the 20 cases referred to above in which operation was ill advised.

Preoperative evaluation of axillary lymph-node involvement was erroneous in 19 per cent, generally in the direction of failure to detect involved nodes. This error is considerably less than that in previous series but emphasizes the inaccuracy of clinical appraisal of the extent of disease.

A hundred and twelve patients (50.4 per cent) were living without evidence of disease from five to eight years after operation. Of the cases without axillary involvement, 75.5 per cent were without recurrence after five or more years, whereas of those with axillary involvement the percentage was 33.3. It should be noted that in the latter group are included the 20 cases referred to above. If operation had been withheld from these cases, cures in the cases with axillary involvement would have been 39 per cent, and the operability rate for the entire group would have been 66 per cent. Although axillary involvement is thus obviously of great significance in the prognosis, it should be noted that when only one or two nodes prove to be involved the prognosis is comparable to that in cases without involvement. Specific notation of involvement of only one or two nodes was made in 15 cases, of which 12 (80 per cent) were in the "cured group." It is primarily in the cases with extensive or numerous axillary metastases that the prognosis is poor.

When the patients are divided into three age groups, it is evident that the prognosis is poorest in

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those younger than forty and most favorable in those over sixty years. The poorer prognosis for the younger group is probably due to the fact that this group presents a greater number of cases with higher grades of malignancy and with axillary metastases already established at the time of operation.

The cases of short duration show a definitely greater curability rate than those of longer duration. It should be observed that the lesions of a high grade of malignancy that are operable are usually of short duration. Hence, the group of short duration always contains a disproportionately large number of extremely malignant lesions, in which the prognosis is poor. The cures in such lesions are predominantly in the group of short duration and it is only in this group that a considerable number with this type of lesion are cured even when the nodes are involved.

The gross characteristics of the primary carcinoma, especially its size, are significant in the prognosis. Thus, five-year survivals were obtained in 89 per cent of cases with lesions less than 2 cm in greatest diameter, in contrast to 18 per cent if the lesions were greater than 4 cm in diameter. The same disparity obtains when cases with or without lymph-node involvement are contrasted. The larger the primary lesion, the greater the incidence of involvement.

The lesions were grouped into three grades of malignancy, according to Greenough's criteria. There were only 11 cases in the lowest grade. None of these presented axillary lymph-node involvement, and cure resulted in all cases. Axillary nodes were involved in 60 per cent of cases with Grade II lesions, and in 65 per cent of the lesions of highest grade. Cure was achieved in 59 per cent of cases with Grade II lesions, including 86 per cent of those without and 40 per cent of those with lymph-node involvement. Cure was obtained in 38 per cent of cases with Grade III lesions, including 57 per cent of those without and 27 per cent of those with nodes. It is obvious that the cases of high malignancy have a poorer prognosis when cases of comparable extent are considered, and it is also evident that a high proportion of these patients present axillary metastases when first seen. Another finding of significance is that local recurrence took place in 18 per cent of cases with Grade III lesions, in contrast to 7.6 per cent of those with Grade II lesions.

Biopsy and immediate pathological examination were performed in 116 cases. Fifty-five of these patients proved to have axillary involvement already present, which suggests that biopsy was resorted to in many cases when the diagnosis was probably clinically obvious. Although the over-all results in the biopsied group show 57 per cent five-year survivals, this favorable showing is doubtless due to the inclusion of a large proportion of the early and

doubtful cases. That the procedure is not entirely free from hazard is shown in the fact that recurrence in the operative field occurred in 15 per cent of the biopsied group, in contrast to 7.5 per cent in the cases not submitted to biopsy.

Recurrences in the operative field may constitute a reflection on the care with which cases are selected for operation and on the operative technic. There was such recurrence in 11 per cent of the present group. As noted above the rate was highest in cases with a high grade of malignancy and also in cases submitted to immediate pathological examination. It is also noteworthy that there is an increased likelihood of operative-field recurrence when the primary carcinoma is large and when axillary metastases are present. Although these findings are not conclusive, they suggest that the extent and character of the primary carcinoma have greater significance than the operative technic.

X-ray therapy has been used as the treatment of choice in inoperable cases and in the treatment of recurrences. Preoperative x-ray therapy has not been employed. Postoperative x-ray therapy was used in a certain number of cases in which the surgeon believed that he had left gross carcinoma after operation, and in some others in which clinical and pathological features augured a poor prognosis. It was not employed routinely in the present series, and it is not demonstrable that any benefit was obtained in the cases in which it was used prophylactically.

#### SUMMARY

This report is the eighth in a series of end-result studies of carcinoma of the breast treated at the Massachusetts General Hospital.

Survivals of five to eight years without recurrence were obtained in 75.5 per cent of cases without axillary lymph-node involvement, in 33.3 per cent of those with axillary metastases and in 50.4 per cent of the entire group submitted to radical operation.

Improvement in curability, as compared with that in previous series of cases, may have been due to better selection of cases suitable for operation, as well as to improved operative technic. Benefits due to shortening of the preoperative duration as a result of educational campaigns were not conspicuous in this series. The occasional employment of postoperative prophylactic radiation does not appear to improve the prognosis.

The presence or absence of axillary lymph-node metastases is of marked significance in the prognosis. Other important factors are the size and duration of the primary lesion, the grade of malignancy and the age of the patient. These factors not only affect the prognosis but also have a bearing on the incidence of operative-field recurrence.

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## PLASMA-VOLUME DETERMINATIONS IN RHEUMATIC SUBJECTS DURING ORAL SALICYLATE THERAPY\*

### Report of a Case with Severe Hemorrhage

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COBURN'S<sup>1</sup> report advocating large doses of salicylates in rheumatic fever aroused widespread interest in the problem of salicylate intoxication. The milder symptoms of nausea, vomiting, tinnitus, deafness and vertigo are considered to be of minor significance. The origin of these symptoms and the action of sodium bicarbonate in alleviating them have been discussed by Smull and her associates<sup>2</sup> and Caravati and Cosgrove.<sup>3</sup> The more serious toxic complications, including death, delirium, dyspnea, acidosis, hypoprothrombinemia and hemorrhage have been investigated by Ryder et al.,<sup>4</sup> Manchester,<sup>5</sup> Owen and Bradford<sup>6</sup> and Jager and Alway.<sup>7</sup> The last investigators suggested the possibility of an increased plasma volume during intensive salicylate therapy because of changes noted in the hematocrit and plasma proteins and by determination of the plasma volume by the dye method in some cases.

Accordingly, 7 rheumatic patients receiving large oral doses of salicylate were studied for changes in the plasma volume.

### MATERIALS AND METHODS

Of the patients studied 6 had rheumatic fever, and 1 had rheumatoid arthritis. The plasma volume, hematocrit and plasma protein concentration, prothrombin activity and salicylate concentration were determined on admission. The patients were then given sodium salicylate orally without sodium bicarbonate in a dosage such that plasma salicylate concentrations of not less than 35 mg per 100 cc were expected.

Plasma volumes were determined by the ten-minute-sample method of Gregersen<sup>8</sup> and Noble and Gregersen,<sup>9</sup> as modified to the use of the Cenco

photometer. A calibrated syringe was used for the injection of the dye T-1824. Duplicate venous hematocrits determined in Wintrobe tubes and plasma protein determinations by the method of Bowman<sup>10</sup> were done on the control and dye samples. The prothrombin time was determined by a modification of the Quick<sup>11</sup> method using thromboplastin prepared from the human brain. The prothrombin activity as a percentage was obtained by comparison with diluted normal human plasmas. Plasma salicylate concentrations were determined by a modification of the method described by Coburn.<sup>1</sup>

The plasma volume, hematocrit and plasma protein concentration, prothrombin activity and salicylate concentration, which were determined at frequent intervals during therapy, are presented, with other relevant data, in Table 1.

### RESULTS

An increase in the plasma volume was noted within ten days after the beginning of oral salicylate therapy in 5 of the patients in this study. Changes in the plasma volume are better expressed as percentage change, in that the actual volume varies with the weight and size of the patient. The increases noted were 38 per cent (1450 cc.) in Case 1, 65 per cent (210 cc.) in Case 3, 16 per cent (550 cc.) in Case 5, 14 per cent (275 cc.) in Case 6 and 11 per cent (340 cc.) in Case 7. A decrease in plasma volume occurred in 2 cases, being 96 per cent (240 cc.) in Case 2 and 40 per cent (80 cc.) in Case 4.

In 8 convalescent patients with no evidence of cardiovascular disease, a series of thirty-four control determinations of plasma volume by the method used in this study showed variations from +4.3 to -6.9 per cent.

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§Kl dye supplied by the Warner Institute of Therapeutic Research, New York City.

The greatest increases in plasma volumes occurred in patients with pre-existing valvular disease who were experiencing salicylate toxicity. Cases 1 and 5 showed evidences of salicylate intoxication by anxiety, severe tinnitus, gross tremor, acidosis (acetonuria and lowered carbon dioxide combining power), lowered prothrombin activity and pul-

owing to poor co-operation on the part of the patient necessitating lower dosages. In the latter there was blood loss, and twenty-four hours after the second plasma-volume determination, clinical shock was evident.

After prolonged sodium salicylate therapy 6 patients showed plasma volumes that were increased

TABLE 1 *Plasma-Volume Determinations and Other Pertinent Data*

CASE No	AGE	SEX	DIAGNOSIS	DATE	PLASMA VOLUME	CHANGE	HEMATOCRIT (WINTROBE METHOD)	PLASMA PROTEIN	SALICYLATE DOSE	PLASMA SALICYLATE CONCENTRATION	PROTHROMBIN ACTIVITY
	yr				cc	%	%	gm /100 cc	gm	mg /100 cc	% of Normal
1	18	M	Aortic and mitral insufficiency and mitral stenosis (functional Grade III*)	5/25	3760	—	47.3	5.9	0.0	0	Less than 10
				5/27	—	—	—	—	8.5	31	37
				5/29	—	—	—	—	8.5	51	22
				5/31	—	—	—	—	8.5	47	20
				6/3	5210	+38.0	45.9	5.9	8.5	51	Less than 10
				6/6	—	—	—	—	4.3	41	43
				6/10	—	—	—	—	4.3	12	45
				6/15	4020	+7.0	40.7	5.7	4.3	15	70
				6/20	—	—	41.5	—	4.3	14	49
				7/6	—	—	—	—	6.0	21	75
				7/9	—	—	—	—	6.0	26	70
				7/12	—	—	—	—	4.0	19	46
2	13	M	Aortic and mitral insufficiency (functional Grade II*)	7/8	2480	—	32.6	4.5	10.0	18	60
				7/10	—	—	—	—	10.0	—	34
				7/12	2240	-9.6	30.0	4.8	6.0	64	12
				7/13	—	—	—	—	3.0	—	Less than 10
				7/14	—	—	—	—	0.0	23	33
				7/15	—	—	—	—	0.0	0	60
				7/19	—	—	—	—	4.0	13	80
				7/24	—	—	—	—	4.0	17	90
				7/29	2690	+8.5	37.7	6.0	4.0	0	—
				—	—	—	—	—	—	—	60
3	15	M	Mitral insufficiency (functional, Grade I*)	6/26	3210	—	42.3	7.4	0.0	—	—
				7/1	—	—	—	—	10.0	13	27
				7/3	3420	+6.5	40.3	7.0	10.0	—	28
				7/5	—	—	—	—	10.0	42	24
				7/9	3120	-2.8	41.7	7.7	10.0	48	—
				8/2	3010	-6.2	43.0	7.0	0.0	—	80
4	15	F	Mitral insufficiency (functional Grade I*)	8/5	—	—	43.2	7.8	0.0	—	—
				6/7	2240	—	38.6	7.8	4.0	3	95
				6/12	—	—	—	—	5.5	11	100
				6/18	2160	-4.0	37.9	7.3	5.5	22	80
5	44	M	Rheumatoid arthritis	6/27	2500	+11.5	38.4	8.4	0.0	0	100
				4/18	3210	—	47.1	5.4	0.0	0	20
				4/23	3420	+6.5	44.7	5.1	12.0	29	—
				4/24	—	—	—	—	16.0	38	—
				4/27	3760	+16.1	40.1	4.8	13.0	37	38
				4/29	—	—	—	—	0.0	6	100
				5/1	3760	+16.1	39.8	4.9	3.0	—	—
				5/14	—	—	—	—	10.0	17	100
				5/22	—	—	—	—	9.0	—	95
				5/28	—	—	—	—	9.0	—	90
				6/1	—	—	—	—	9.0	13	—
				6/8	—	—	—	—	4.0	—	80
6	16	F	Mitral stenosis and insufficiency (functional, Grade II*)	6/20	3330	+3.7	39.9	4.5	4.0	—	65
				5/1	1935	—	39.5	8.0	0.0	0	100
				5/4	—	—	—	—	12.0	46	—
				5/6	2210	+14.0	35.6	7.4	12.0	57	Less than 10
				5/7	—	—	—	—	0.0	32	50
				5/8	—	—	—	—	0.0	—	60
				5/10	—	—	—	—	0.0	3	100
				5/15	2320	+19.0	34.7	7.0	0.0	0	—
				6/19	2210	+14.0	31.0	6.9	0.0	0	—
				—	—	—	—	—	—	—	85
7	14	F	Mitral stenosis and insufficiency (functional, Grade III*)	7/25	—	—	—	—	1.3	0	70
				8/2	2160	—	41.3	6.8	5.0	17	48
				8/5	—	—	—	—	5.0	29	50
				8/9	2500	+11.1	39.8	6.9	5.0	30	65
				8/16	—	—	—	—	8.0	48	57
				8/23	2320	+7.4	39.8	6.7	6.4	45	31
				8/29	—	—	—	—	6.4	47	39
				9/6	—	—	—	—	6.4	33	55
				9/13	2210	+2.3	43.9	—	6.4	37	—

\*Functional capacity based on criteria outlined by the Criteria Committee of the New York Heart Association.

monary congestion (basal rales) at the time the second plasma volume was determined. In Case 6 the same symptoms and signs were demonstrated, but the carbon dioxide combining power was not measured. One patient (Case 3) never had more than mild symptoms of intoxication.

Decreased plasma volumes occurred in Cases 2 and 4. In the former the salicylate concentration in the blood never exceeded 22 mg per 100 cc,

from the initial values. The average increase was 9 per cent. One patient (Case 3), who was treated in an original monocyclic attack of acute rheumatic fever and who showed an increase of 6.5 per cent in plasma volume after a week of intensive oral salicylate therapy, had a return of the plasma volume to the original level while continuing the salicylate. When rechecked two weeks after the last dose of drug a plasma volume 6 per cent less than that on

admission was found. In the remaining 5 cases, once the increase had occurred, the plasma volume remained at an elevated level even after all medication had been omitted, and only slowly returned toward the initial value.

From our data it is evident that the hematocrit and plasma protein determinations did not consistently reflect the changes in plasma volume as measured by the dye method.

Changes in the prothrombin activity in 6 patients followed a rather irregular pattern. In the main, however, whenever a plasma salicylate concentration of over 35 mg per 100 cc was present, there was a definite and persistent depression of the prothrombin activity. Hemorrhagic episodes were not observed in any case except in Case 2. One patient (Case 1) had a prothrombin activity of 0 on admission, but it could not be established whether or not salicylates had been administered before admission. Another patient (Case 2), whose prothrombin activity had progressively decreased while he was receiving massive doses of salicylate therapy orally, developed severe intoxication and hemorrhage. This case is reported in detail below.

### CASE REPORT

D V., a 13-year-old boy, was admitted to the hospital with a history of repeated episodes of nasal bleeding and painful swelling of the joints of brief duration. He had had rheumatic fever 3 years previously, when he had been treated with prolonged bed rest; he had subsequently been limited in school athletics because of a heart murmur.

Physical examination revealed a well developed and well nourished boy, who appeared ill and obviously favored the left knee. There was mild injection of the pharynx. The lungs were clear. The apical impulse was heaving and palpable in the fifth left interspace in the midclavicular line. The left border of cardiac dullness fell at the same point. The rhythm was regular, and the rate rapid. There was a soft, blowing systolic murmur at the apex and harsh systolic and blowing diastolic murmurs at the base and along the left sternal border. The abdomen was soft and nontender, and the liver and spleen were not palpable. The left knee and, to a lesser degree, both ankles were red, hot, tender and swollen.

The temperature was 102 F and the pulse 120; the blood pressure was 120/60.

The patient had obviously received salicylates before admission since the blood salicylate concentration was 15 mg per 100 cc and the prothrombin activity was 60 per cent. He was given 10 gm of sodium salicylate daily by mouth. A prompt clinical response occurred within 24 hours. This dosage was continued for 4 days, when nausea and anorexia, anxiety, a gross tremor, flushing and sweating, an increased respiratory rate without dyspnea and a few fine rales at the right base first appeared. The carbon dioxide combining power was 40 vol. per cent, and a urinalysis was negative except for a + test for acetone. The plasma salicylate concentration was 64 mg per 100 cc and the prothrombin activity 12 per cent of normal.

On that day of treatment bleeding from the nose was first noted but did not appear to be severe since the amount of blood was small and examinations of the posterior pharynx did not suggest that any great amount of blood was being lost by this route. During the afternoon the patient vomited once, and there was no gross blood in the vomitus. Vomiting recurred on the following morning; its appearance suggesting old blood to the nurse, but the specimen was discarded. Throughout the 5th day there was intermittent nasal bleeding and 6 gm of sodium salicylate was given. A plasma-volume determination was 9.6 per cent (240 cc.) less than that on admission. The nasal bleeding continued during the night. On the following day the patient appeared listless and

pale and complained of nausea and malaise. Salicylates were omitted. During the early evening the patient fainted in bed. He immediately regained consciousness, and examination revealed no evidence of nasal bleeding at that time. The blood pressure was 110/45. Shortly thereafter the patient vomited 600 cc of bright red, loosely clotted blood. An hour later a similar amount was vomited and the blood pressure was 94/40. The prothrombin activity at that time was reported as less than 10 per cent. The patient was immediately given molar sodium lactate and 64 mg of menadione bisulfite intravenously, as well as 500 cc of fresh whole blood. A third vomiting of 500 cc of bright red blood occurred before transfusion. Two hours after the transfusion the blood pressure was 120/40; no further evidence of bleeding occurred. Further transfusions were given on the following 2 days. On the 3rd day after the last dose of salicylate, the plasma salicylate concentration was 0 and the prothrombin activity was 60 per cent of normal. The patient was asymptomatic at that time. Twenty-four hours later the temperature reached 103 F, and he complained of abdominal pain, dryness of the throat and a desire to cough. The chest was clear but the abdomen was diffusely tender with rebound tenderness but no localizing signs. Sodium salicylate was resumed with a daily dose of 4 gm orally, and the administration of 25,000 units of penicillin every 3 hours prophylactically was begun. A prompt amelioration of symptoms resulted. Penicillin was continued for 8 days and the salicylates were increased to 5 gm daily. The prothrombin activity remained within normal limits. Thereafter, convalescence was uneventful. A plasma volume determined 16 days after the hematemesis and transfusions was increased 8.5 per cent (450 cc.) over the initial volume. The plasma salicylate at that time was 17 mg per 100 cc.

### DISCUSSION

From this study of 7 patients who received oral sodium salicylate therapy it is evident that the plasma volume tends to increase at some point during the course of treatment. A possible explanation for this may be found in the study of Lyons, Jacobson and Avery,<sup>12</sup> who demonstrated a significant increase in the plasma volume in 14 normal subjects who received large amounts of sodium chloride or sodium bicarbonate by mouth. It is our hypothesis that with large doses of sodium salicylate enough sodium may be ingested to result in a measurable increase in the plasma volume. In patients receiving both sodium salicylate and sodium bicarbonate such an effect would be even more reasonable.

In Case 1 a prompt increase in the plasma volume of 38 per cent was noted. This increase was coincidental not only with signs of salicylate toxicity but also with clinical evidence of increasing heart failure. This patient, with pre-existing aortic and mitral valvular disease and a recurrence of acute rheumatic fever, was admitted in mild chronic congestive failure. He showed an initial high plasma volume. This is consistent with the reports of Gibson and Evans,<sup>14</sup> Seymour et al.<sup>15</sup> and Warren and Stead.<sup>16</sup> In such cases the addition of more sodium ions through the medium of sodium salicylate therapy may have been the basis for a further increase in plasma volume and a coincident increase in heart failure.

### SUMMARY

Definite increases in plasma volume occurred in 6 of 7 patients studied during oral sodium salicylate therapy.



The degree of prior valvular damage, together with the acute disease and the added sodium ions of the drug, appear to be the factors responsible for the increase in plasma volume

When plasma salicylate concentrations were maintained in the range of 35 mg per 100 cc, an associated depression of prothrombin activity was found

One case is presented in detail because of the occurrence of a severe hemorrhage, associated with a marked hypoprothrombinemia

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## MEDICAL PROGRESS

### HEMATOLOGY (Concluded)\*

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#### HEMORRHAGIC DISEASES

As previously stated the hemorrhagic diseases may be classified as those due to a defect, usually a reduction, in the blood platelets, to a defect in the coagulation factors of the blood and to a disturbance of the capillaries<sup>91</sup>

#### Thrombocytopenic Disorders

Qualitative abnormalities of the platelets undoubtedly exist, but they are exceedingly rare as compared with quantitative changes. Marked reductions in blood platelets (thrombocytopenia) occur in a number of conditions and may be due to bone-marrow disease, such as hypoplasia, aplasia, leukemia or other infiltration, deficiency of liver-extract principle (pernicious anemia), iron or certain components of the vitamin B complex including folic acid, to the hypersplenism of splenomegaly that is caused by cirrhosis of the liver, chronic infectious splenomegaly, disorders of lipid cellular

metabolism and other conditions, allergic reactions to drugs and foods; various conditions, usually infectious diseases but with the bone-marrow picture as seen in the idiopathic group mentioned below, and unknown disorders usually associated with the "hypersplenism" of an abnormal spleen and generally requiring removal (idiopathic thrombocytopenia)

In thrombocytopenia due to actual disease of the bone marrow, whether hypoplasia, aplasia, leukemia or neoplastic infiltration, the sternal-puncture aspiration of the marrow shows great diminution or complete lack of megakaryocytes. In idiopathic thrombocytopenia megakaryocytes are numerous. Thus, a simple puncture-aspiration biopsy of the sternal marrow is of great value in differentiating the two types of disturbance.

Thrombocytopenic purpura as a complication of an acute infectious or exanthematous disease is fairly common. This is particularly true of children. Kaufman<sup>92</sup> reports the cases of 2 children who developed thrombocytopenic purpura after scarlet fever. The second case showed 8 per cent eosinophils in the blood. Unfortunately, sternal-marrow examinations were not done. Methionine and foods high

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in this amino acid were used for treatment with prompt cessation or diminution in the hemorrhagic tendency. Further trial with this therapeutic method is desirable. Two cases of German measles complicated by thrombocytopenic purpura are reported by Warren, Rogliand and Potsbay.<sup>42</sup> Uneventful recovery ensued in both, as it almost always does in cases associated with an acute infection. In a case of infectious lymphadenitis (mononucleosis) presented by Dameshek and Grassi,<sup>43</sup> however, the thrombocytopenia and bleeding were so marked that splenectomy had to be resorted to and was followed by dramatic recovery. It was thought that the large spleen that was present was contributing to the development of marked "hypersplenism" and thus to the thrombocytopenia. Thrombocytopenia occurring in the course of malaria is reported by Schragar and Kean.<sup>44</sup> This is extraordinarily rare, occurring perhaps once in 10,000 cases of the disease.

Boeck's sarcoid with thrombocytopenic purpura is reported by Enzer<sup>45</sup> and by Nordland et al.<sup>47</sup> In Enzer's case there was generalized sarcoidosis with splenomegaly and pancytopenia. Splenectomy was followed by uncontrollable hemorrhage, which led to death. On the other hand, I have seen cases of Boeck's sarcoid of the spleen in which splenectomy led to a complete recovery in the platelet level and cessation of bleeding. Nordland and his associates<sup>47</sup> observed a similar case in which what appeared to be typical fulminating idiopathic thrombocytopenic purpura developed during the fifth month of pregnancy. Splenomegaly was present, however, and was difficult to explain, since in the idiopathic disease the spleen is hardly ever enlarged. The spleen was removed and showed Boeck's sarcoid, and the patient made an uneventful recovery. The author discusses 13 cases of idiopathic thrombocytopenic purpura, 7 with splenectomy during pregnancy. Patterson<sup>48</sup> reports a case of idiopathic purpura occurring during pregnancy in a twenty-two-year-old primipara with a strong family history of hemorrhagic disease. Bleeding manifestations began during the fifth month of pregnancy, and postpartum bleeding was excessive. The newborn infant developed purpura and bleeding in the stools and showed a platelet level of 18,000. Both the mother and the infant subsequently recovered. This case is worthy of comment for several reasons: the occurrence of thrombopenic purpura in the infant of a thrombopenic mother indicates the possibility of a circulating antiplatelet growth factor, which is consistent with the conception, expressed below, of a splenic factor that enters the blood stream and causes inhibition of megakaryocytes, and the question is open whether conservative treatment was justified in this case even though it worked out happily, since the mother might have bled uncontrollably at delivery. Had splenectomy been performed at the fifth month, the baby would not

have developed thrombocytopenia, and the maternal bleeding would have been minimal at delivery.

Some cases of the hypersplenism caused by splenomegaly continue to be reported as idiopathic thrombocytopenic purpura. Splenomegaly is often associated with leukopenia, neutropenia, thrombocytopenia and anemia.<sup>41</sup> There is either pancytopenia or a selective cytopenia or group of cytopenias. The splenomegaly may be due, as noted above, to Boeck's sarcoid, chronic infections of the spleen, cirrhosis of the liver, splenic-vein thrombosis, Gaucher's disease or unknown causes. Splenectomy usually brings the blood picture back to normal whatever the underlying condition. Suchacki and Glass<sup>49</sup> report the case of a Nigerian Negro with a large spleen in whom marked hemorrhagic manifestations (diagnosed as idiopathic thrombocytopenic purpura) were present. The blood showed pancytopenia. Splenectomy was followed by a dramatic response.

Dameshek and Miller<sup>100</sup> discuss the sternal-marrow findings with particular reference to the megakaryocytes in idiopathic thrombocytopenic purpura, which they regard as a form of hypersplenism. The blood in this condition is characterized by an extreme reduction in platelets. Paradoxically, however, the platelet precursors in the marrow—that is, the megakaryocytes—are increased. Careful histologic study of the megakaryocytes demonstrated a greatly diminished platelet production. After splenectomy platelet production became extraordinarily marked, indicating that before splenectomy something had been inhibiting platelet production from megakaryocytes. Since splenectomy resulted in correction of this defect, the spleen was suspected of being the site of an abnormal material or an abnormal amount of normal material causing megakaryocytic inhibition. The disorder was thus thought to be a form of hypersplenism with enlargement of the spleen. The diagnostic value of the sternal-puncture test in the differentiation of idiopathic and other forms of purpura is discussed.

Schwartz<sup>51</sup> reports the bone-marrow findings in idiopathic thrombopenic purpura, with particular reference to the concentration of eosinophils and their diagnostic and prognostic significance. He observed that when more than 50 eosinophils were found per 1000 granulocytes the patient usually made a spontaneous recovery without splenectomy. These cases were thought to be of allergic nature. There can be no question that an allergic reaction—whether to an infection, drug or food—results in a megakaryocytic reaction, with a reduction in platelets. Schwartz's contention that the finding of marrow eosinophils is definitely indicative of such a reaction cannot yet be definitely proved.

Aggeler, Howard and Lucia<sup>52</sup> discuss their data on platelet counts as related to bleeding time, coagulation time, capillary fragility and degree of

clot retraction in 64 normal subjects and in 404 patients suffering from various diseases. The counts are of distinct value if done by the same person day after day. Parenthetically, it may be said that platelet counts performed only occasionally are best not done at all, since they are subject to great inaccuracy. Estimation of the number of platelets on a well spread cover-slip smear is much better than the occasionally performed platelet count. Aggeler et al found a statistically significant relation between the platelet count, the bleeding time and the clot retraction. In the stage of recovery from idiopathic thrombocytopenic purpura there may be some dissociation between these factors.

A peculiar type of thrombopenic purpura associated with hemolytic anemia and generalized platelet thrombosis is described by Trobaugh and his associates<sup>103</sup>. Death occurred two weeks after the onset of illness. At autopsy widespread platelet thrombi were present in small blood vessels throughout the body. About 15 similar cases have already been recorded. Graña<sup>104, 105</sup> reports the experimental production of thrombopenic purpura in dogs and guinea pigs by the injection of heterophil antibody of the Forssman type. Not only was the platelet count depressed but also the capillary walls showed evidence of injury. This paper points to the possibility of an abnormal agglutinating mechanism in the pathogenesis of some cases of idiopathic thrombocytopenic purpura. Skelton and his co-workers<sup>106</sup> found that alpha tocopherol (vitamin E) prevented or cured the picture of experimental thrombocytopenic purpura of antiplatelet serum. This material was apparently used with beneficial results (although detailed statements are not made) in 5 cases of idiopathic thrombocytopenic purpura and in 5 cases of other types of purpura. This form of therapy requires further study.

A case of thrombocytopenic purpura due to potassium iodide administration is reported by Davis and Saunders<sup>107</sup>. Discontinuance of the drug resulted in subsidence of the purpura, and experimental reproduction was achieved later by a single administration of 0.5 gm. The development of purpura during heat stroke was studied by Wright, Reppert and Cuttino<sup>108</sup>. The hemorrhagic disturbance was apparently the end result of both thrombocytopenia and a decrease in prothrombin concentration of the blood, the latter being due probably to extensive hepatic damage. Bone-marrow smears revealed no abnormalities of the megakaryocytes.

#### *Defects in Coagulation Factors*

**Hypoprothrombinemia** The most frequent coagulation defect is that involving prothrombin. Quick<sup>109, 110</sup> emphasizes repeatedly that his original methods for the preparation of thromboplastin and for performing the prothrombin test have been considerably modified, leading in many cases to

inaccurate results. Aggeler and his associates<sup>111</sup> present a critical analysis of the Quick test for prothrombin and conclude that the use of a single specimen of blood from one normal subject as a normal standard may lead to considerable error. To establish reliable normal standards, the blood of at least 5 normal subjects should be individually tested with the same specimen of thromboplastin, and the results averaged. It is suggested that a carefully prepared and stored dehydrated human brain is a more potent source of thromboplastin than the average rabbit brain.

The development of hypoprothrombinemia during salicylate therapy appears to be a definite phenomenon. Govan<sup>112</sup> reports his studies of 24 children receiving salicylates, mostly aspirin. In 6 cases an abnormal prolongation of the prothrombin time occurred. The most marked changes occurred between the second and fifth days of medication. Despite continuation of salicylates, the prothrombin time returned to normal values by the ninth day. Owen and Bradford<sup>113</sup> studied 25 adults with rheumatic fever who received 10 gm of salicylates intravenously daily. The prothrombin levels fell to 10 to 59 per cent of normal within one to six weeks. Bleeding in the form of epistaxis or splinter hemorrhages occurred in 5 cases at the time of maximum prothrombin depression. Clausen and Jager<sup>114</sup> attempted to correlate the degree of hypoprothrombinemia with plasma salicylate levels rather than with the total daily dose. A direct correlation was found in both human beings and animals between the height of the plasma salicylate level and the degree of hypoprothrombinemia. Significant reductions in the prothrombin level (to 40 per cent of normal) did not occur until plasma salicylate levels of at least 600 microgm per 100 cc were reached, varying doses of salicylates being required for this purpose.

Prolongation of the prothrombin time by quinine was reported by Pirk and Engelberg<sup>115</sup>. Quick<sup>116</sup> studied this matter further and found no such prolongation. He also showed that the administration of vitamin K in large doses did not cause a hyperprothrombinemia. In this article Quick attempts to discredit further use of the term "hypoprothrombinemia."

A diminution in circulating prothrombin (increased prothrombin time, hypoprothrombinemia) occurs not only in obstructive jaundice and hepatitis but also in severe dietary inadequacy, in chronic diarrhea and in pregnancy. Rapoport and Dodd<sup>117</sup> report 7 cases of hypoprothrombinemia in infants with prolonged diarrhea. The hemorrhagic manifestations and the prothrombin levels were adequately controlled by the parenteral administration of vitamin K.

Meyers and Poindexter<sup>118</sup> studied the prothrombin levels in patients with both occlusive coronary disease and angina pectoris. Coronary occlusion

produced a definite shortening of the prothrombin time within twenty-four to seventy-two hours after the beginning of the attack and lasting for several weeks. This abnormality may be due to a release of excess thromboplastin from injured heart muscle and perhaps by disintegration of platelets in the mural thrombus.

Ogura et al.<sup>118</sup> studied 27 cases of coronary occlusion by the Waugh-Ruddick test and demonstrated accelerated prothrombin time in 78 per cent of cases. This occurred beginning with the second or third day and continued until the seventeenth day. The technic of the Waugh-Ruddick test is described in the article. Cotlove and Vorzimer<sup>119</sup> observed the prothrombin time in 76 cardiac patients and found that no alterations in this test occurred in either coronary occlusion or angina pectoris. (These contradictory findings have no particular bearing on the use of dicoumarol for the treatment of coronary thrombosis, as suggested by Wright and his associates.<sup>120</sup> Whether the use of dicoumarol represents good medical practice is not yet completely certain.)

Scherf and Schlachman<sup>121</sup> studied the prothrombin time in 22 cardiac patients receiving methylxanthines such as aminophylline and theobromine and found a shortening of the prothrombin time. Whether these results have any definite significance is questionable, in view of the undoubted limitations of the present tests for prothrombin. An attempt to introduce a good deal more accuracy into the present tests for prothrombin has been made by Deutsch,<sup>122</sup> who devised a photoelectric method for studying thrombin. This method deserves further investigation. Levy and Conroy<sup>123</sup> recorded the blood prothrombin (by the Smith bedside test) in patients receiving anesthesia. Ether anesthesia shortened the prothrombin time and therefore may be of some importance in the causation of post-operative thrombosis.

**Hemophilia.** Tocantins<sup>124</sup> reviews the various factors having to do not only with coagulation but also (which is quite as important) with preventing blood from clotting within the circulation. The coagulants are well known and include thromboplastin (cephalin), prothrombin and fibrinogen. The anticoagulant factors are less well known and may be listed as follows: an intact vascular endothelium, antithromboplastin, antithrombin and fibrinolysin. Blood clotting may be enhanced either by an increase in coagulation factors or by a decrease in anticoagulant factors. Tocantins believes that hemophilia is due to an excess of anticephalin (antithromboplastin) activity and not to a diminution in a thromboplastin-plasma material as maintained by the various workers at the Thorndike Memorial Laboratory of the Boston City Hospital. Lewis et al.<sup>125</sup> review their studies of the past decade in the physiopathology of hemophilia and conclude that the disease is due to a great deficiency in a

globulin fraction of the plasma, which may be called the "antihemophilic globulin." In this paper, allusion is also made to Tagnon's work on the presence in normal plasma of a proteolytic fibrinolytic enzyme, having as yet unidentified role in blood coagulation. Tagnon and his co-workers<sup>126</sup> contribute another article dealing with the fibrinolytic enzyme chiefly in hemorrhagic shock. Munro,<sup>127</sup> in common with Tocantins in this country and Pavlovsky in Buenos Aires, found an anticoagulant substance in the blood of a hemophilic patient. The anticoagulant was found not to be antiprothrombin, heparin or antithromboplastin but was a lipoprotein apparently identical with the anticoagulant described some years ago by other observers. Fantl and Nance<sup>128</sup> found a circulating anticoagulant in the blood of a woman with severe hemorrhagic disease and a greatly prolonged coagulation time. It was determined that the material was an antithromboplastin.

The treatment of hemophilia has measurably advanced but not yet to the goal of complete control. Thrombin or fibrin foam will control to a large extent minor local bleeding, such as that from the gums, dental sockets, nose and skin, and even major operations have been performed with the use of these materials.

Employment of the antihemophilic globulin derived from the plasma fractionation program of Harvard Medical School has demonstrated a striking effect on the bleeding of hemophilia when only 100 to 200 mg. of the material is given intravenously. The daily use of this substance, however, is impractical. Van Creveld and Mastenbroek<sup>129</sup> present a preliminary report on a hemophilic patient in whom the administration of 24 cc. of a 2 per cent solution of this fraction promptly reduced the coagulation time to normal and maintained it so for forty-eight hours.

The extraordinarily rare afibrinogenemia, which is usually congenital, is considered by Pinniger and Prunty.<sup>130</sup> In a case of severe hemorrhagic disease in a girl, these observers found a greatly prolonged clotting time and an almost complete lack of fibrinogen. Transfusion of reconstituted dried plasma was effective in controlling the bleeding and improving the fibrinogen deficiency. Rocha e Silva and his associates<sup>131</sup> demonstrated a great reduction in circulating fibrinogen in experimental shock produced by trypsin, peptone and ascars extracts.

#### *Hemorrhagic Capillary Disorders*

Undoubtedly, the most frequent of the hemorrhagic disorders are those due to abnormalities of the capillaries. These occur in infectious diseases, deficiency states, at times with endocrine disorders and congenitally or idiopathically. The "devil's pinches" in soft-skinned women are often the cause for alarm but in reality have little if any significance. Whether they have anything to do with an

excess of circulating estrogen is questionable. All the various hemorrhagic factors in these cases, including platelets, prothrombin, clotting and bleeding factors, are normal. In rheumatic fever and acute glomerulonephritis purpuric manifestations are not rare. The platelets are normal, but apparently there is a more or less generalized disorder of minute blood vessels with seepage into the skin. Jones and Moore<sup>132</sup> discuss 3 such cases. Montgomery<sup>133</sup> found a definite increase in capillary fragility. No effect on the hemorrhagic disturbance or the capillary fragility was obtained with the use of vitamin P (derived from paprika).

A hemorrhagic disorder of mucous membranes with the formation of bullae and vesicles is reported by Foley<sup>134</sup> in a group of American and British prisoners of war confined to a Japanese prison camp. Crops of vesicles and hemorrhagic bullae developed on the buccal, palatal and tonsillar mucosa. No skin manifestations were present, and all the tests for hemorrhagic disturbance were negative. There was a quick response to the use of a high-protein, high-fat diet, but vitamins of various sorts were of no value. In occasional cases of hemorrhagic capillary disease one can make the diagnosis of Henoch-Schönlein purpura. In the Henoch type hemorrhagic manifestations are associated with intestinal disturbances, which may include abdominal pain, hematemesis and melena. Such a case is reported by Whitmore and Peterson.<sup>135</sup> In the Schönlein type joint manifestations are present. Since purpura, joint manifestations and intestinal disturbance may all coexist the designation of Henoch-Schönlein purpura is justified.

A hereditary capillary defect is that known as hereditary hemorrhagic telangiectasia. Kushlan<sup>136</sup> reviews the historical and clinical aspects of the disorder and reports a case. The newly introduced material called rutin was used in a dosage of 40 mg daily by mouth. There was "prompt" cessation of epistaxis, of gum bleeding and, finally, of gastrointestinal bleeding. The patient had been maintained for several months on a daily dosage of 20 mg of rutin.

During the past year a number of articles dealing with rutin have appeared. This is a crystalline glucoside of quercetin derived from buckwheat leaves and flowers, tobacco leaf, rue herb and many other plants. Chemically, it is a derivative of flavone and related closely to hesperidin (vitamin P), citrin and ascorbic acid. It appears to have no toxic manifestations. Shanno<sup>137</sup> used the material in a variety of cases showing increased capillary fragility, and in all cases except those with thrombocytopenic purpura and allergic purpura there was a return to normal of the capillary fragility following the use of the drug. In a report to the Council on Pharmacy and Chemistry of the American Medical Association, Smith<sup>138</sup> takes this and other articles on rutin to task. The procedures for measuring

capillary fragility are crude, and there is no complete agreement among the workers in the field on the reliability of the methods. It is probable that before another year has passed, the results with rutin therapy will have been fully assessed.

A queer hemorrhagic disorder characterized by a prolonged bleeding time is that of pseudohemophilia. The tendency to unusually profuse and continued bleeding after minor trauma resembles the bleeding of hemophilia. In about half the cases a definite family history of profuse bleeding in both females and males is obtained, with transmission by either sex. In such a case reported by Perkins<sup>139</sup> there was uncontrollable bleeding after minor operative procedures, and the development of large ecchymoses with slight trauma. The history of bleeding could be traced through five generations, and there was transmission from father to son. In addition to the abnormal bleeding time, a failure of capillary retraction (as previously noted by MacFarlane) was observed by means of capillary microscopy. Estren, Sanchez Médal and Dameshek<sup>140</sup> review the subject of pseudohemophilia and their experiences with 11 cases. The literature, clinical and laboratory features, diagnosis and therapy, together with a critical review of methods for the study of hemorrhagic disorders, are presented. The disorder, which is by no means rare, appears to be due to a congenital or hereditary defect of capillary retractility. In some ways it is more difficult to treat than hemophilia itself, since transfusions of blood are ineffective.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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#### CASE 33391

##### PRESENTATION OF CASE

A twenty-three-year-old man entered the hospital in shock

About five years before admission the patient had several spells of unconsciousness, which at that time were thought to be petit-mal attacks. Systolic murmurs were noted at the base of the heart on several examinations thereafter. Four months prior to entry he began to experience throbbing frontal headaches, upper respiratory infection, with coryza, mild soreness of the throat and a cough productive of small amounts of sputum. At about the same time he began to have soreness of the left shoulder radiating down the arm for a short distance. Three weeks later there were several episodes of epistaxis, and he was given a sulfonamide for a week, during which time he had night sweats but no fever or chills. The soreness of the shoulder and other symptoms persisted, and he was admitted to another hospital one month after the onset of symptoms, or three months before admission to this hospital.

Examination at the other hospital revealed a pericardial friction rub but no valvular murmurs. An electrocardiogram showed flattening of the T segments in Lead 1, with inversion of the T waves in Leads 2 and 3. X-ray films of the chest revealed generalized enlargement of the heart, with thin arcuate calcifications overlying the left border. On admission the sedimentation rate was 65 mm per hour, two and a half weeks later it was 35 mm. A blood culture was negative. The nonprotein nitrogen was 53 mg per 100 cc. The Mosenthal test was normal. In the hospital the temperature fluctuated between 98 and 102°F for thirty-five of the forty days he remained there. On the third day another x-ray film of the chest showed a marked increase in the size of the heart shadow, with increase of the pulmonary vascular markings. Symptomatically he improved considerably while taking salicylates, and they were continued throughout his stay, except for a period of one week. On the last three days in the hospital the pericardial fluid had subsided to such an extent that an apical systolic blow and a low rumbling diastolic blow were heard, the latter in the lateral decubitus position. He was dis-

charged home, where he remained on salicylates for several weeks and continued to improve, regaining both strength and ambition.

Three weeks before entering the Massachusetts General Hospital, the patient had a mild upper respiratory infection with cough, nausea and vomiting. He also complained of soreness over the right upper quadrant of the abdomen. Two weeks later he re-entered the outside hospital, complaining of moderate dyspnea and slight edema of the feet, ankles and legs, which disappeared after a few hours' rest in bed. There was mild but definite cyanosis. Physical examination revealed pleural fluid bilaterally. The heart beat was regular at 130, no friction rub and no murmurs were audible. An x-ray film of the chest showed fluid in both pleural cavities, more on the right side than on the left, with collapse of the right middle and lower lobes. The heart shadow was considerably smaller than at the original examination.

Examination of the blood revealed a red-cell count of 5,000,000, with a hemoglobin level of 100 per cent, and a white-cell count of 8700, with 68 per cent neutrophils. The nonprotein nitrogen was 44 mg per 100 cc. The urine gave a + test for albumin, and the sediment contained 3 to 5 red cells per high-power field. Six sputum specimens and the chest fluids were negative for acid-fast bacilli. Beta-hemolytic streptococci, alpha-hemolytic streptococci and *Staphylococcus aureus* grew from the sputum cultures. The chest fluid was sterile.

Two days after admission it was obvious that there was an increasing venous pressure, with engorgement of the neck vessels even in the sitting position. There was a paradoxical pulse. The systolic blood pressure was 105, the diastolic point was difficult to determine, but was thought to be 95. The pleural fluid had increased bilaterally. The liver was palpable three fingerbreadths below the costal margin but was nontender. There was a productive cough, and later the sputum became bloody. Paracenteses were performed twice on the right, with marked improvement in the respirations, although the venous engorgement persisted. A third paracentesis produced 800 cc of fluid, this time without the improvement that had been noted previously. On the seventh hospital day an attempt was made to obtain pericardial fluid. On inserting the needle into the fifth left interspace near the sternum, a definite grating sensation was felt just as the needle came in contact with the heart. Five cc of blood-tinged fluid was obtained. Another attempted paracentesis a little farther laterally in the same interspace failed to obtain fluid.

On the day of the pericardial paracentesis the patient was transferred to this hospital.

On arrival, he was breathing with great distress and was cyanotic, anxious and confused. Cyanosis was most marked in the hands and feet. The blood pressure and pulse were unobtainable. The skin was clammy. The neck veins were slightly distended,

without visible pulsations. Veins over the extremities were collapsed. The cardiac apical beat was not palpable, but to percussion the heart seemed enlarged about 10 cm. to the left of the midsternal line. The sounds were distant but regular at a rate of 80. There were dullness and decrease of breath sounds over both bases. No rales were heard. The liver extended 3 to 4 cm. below the costal margin and was tender. The sacral and scrotal regions were edematous. No reflexes could be obtained.

An x-ray film of the chest showed fluid in the left pleural cavity. The heart shadow had not changed since the last examination.

Two attempts were made to tap the pericardium through the xiphoid approach shortly after admission. No pericardial fluid was obtained. Death occurred a few hours after entry.

### DIFFERENTIAL DIAGNOSIS

DR GEORGE W. PICKERING\* This is quite clearly a case of acute pericarditis in a man of twenty-three. I suppose the possible causes of acute pericarditis in such an individual are first, rheumatic fever, second, tuberculosis and, third, some rather less common ones, such as a septic condition, an infarct of the heart and uremia. Cardiac infarct can be excluded. Uremia can also be ruled out without further discussion because of the blood chemistry and the subsequent course. I think that we can also exclude sepsis. We are not given any details about the pericardial fluid, but we know that the pleural fluid was sterile, that the blood culture was sterile and that there was no leukocytosis. That leaves, as the chief possibilities, rheumatic and tuberculous pericarditis.

Let us begin with the first episode, which is in the past history. He had a number of petit-mal attacks or, rather, attacks of unconsciousness that were thought to be petit-mal attacks. Unfortunately, we know very little about these attacks. We know nothing about the duration, the frequency and so forth, whether they were preceded by an aura, or whether they were preceded by any definite events in his environment. In other words, were they dizzy attacks or were they true petit-mal attacks? If they were epileptic attacks, we have no family history or symptoms of a cerebral lesion. I had thought this might possibly fit into tuberculosis — that these attacks might result from a tuberculoma of the brain. But I do not believe that we can say any more than that.

The next episode that he had was at the age of eighteen. He is now twenty-three and comes in with fever and upper respiratory infection and soreness of the left shoulder, which to my mind sounds like pain due to involvement of the phrenic nerve, but there is no evidence in the history of increase of pain with respiration, such as one gets in many cases when the diaphragm itself is involved, particularly on the pleural side. Then the signs on ad-

mission show quite clearly that he had an acute pericarditis. There was a friction rub, followed by enlargement of the heart shadow. This is actually the first x-ray film. There is a peculiar feature here, a thin arcuate calcification overlying the left border of the heart shadow. These are just visible but they are possibly about 3 or 4 mm. in from the edge of the heart shadow. It is tempting to speculate on these. They are not due to old cardiac infarction. They do suggest possibly that there had been a pre-existing pericarditis, and I should have guessed that tuberculosis was the cause of that. This film shows enlargement of the heart shadow, probably due to pericardial fluid, although I am not expert on radiologic diagnosis. This was obviously regarded at the time as rheumatic and was treated by salicylates. It is stated that he improved considerably while taking salicylates, but it is also stated that the temperature ranged between 98 and 102°F for thirty-five out of his forty days in the hospital, and my interpretation is that he did not respond to salicylates. That, I think, is the first point against rheumatic fever as a diagnosis. The second is that this was an adult, in most adults one would expect some symptoms and signs in the joints, but those were absent. There is one other point that I should like to comment on if this were an effusion into the pericardium, I should have expected at that time that a marked increase in venous pressure would have been noted in the neck. There is no mention of that in the record. Then we come to the noises that were heard in the heart. After the fluid had started to subside, an apical systolic blow and a low, rumbling diastolic blow were heard, the latter in the lateral decubitus position. Did this mean valvular disease? I think Dr Paul D. White and Dr T. Duckett Jones<sup>†</sup> have shown here that one can get diastolic murmurs associated with cardiac enlargement. Does that then mean cardiac enlargement in this case, quite distinct from the pericardial fluid? If it does, then it argues for involvement of the heart muscle, which is strongly in favor of rheumatic heart disease. On the other hand, I think that it is rather difficult sometimes to distinguish a pericardial rub from a murmur, and I am not at all sure this may not have been a to-and-fro rub as opposed to the apical diastolic and rumbling diastolic blow reported.

The patient then went home and shortly afterward returned to this same hospital, where he was found to have signs of venous congestion. At any rate, he had edema, although it is stated that the venous pressure did not rise until two days after admission. I suspect that it was present on admission. He had fluid in both pleural cavities, with collapse of the right middle and lower lobes. He did not have anemia, the hemoglobin being 100 per cent, that is against rheumatic disease. There

<sup>†</sup>Blond, L. J., White, P. D., and Jones, T. D. Development of mitral stenosis in young people: discussion of frequent misinterpretation of mitral diastolic murmur at cardiac rest. *Am Heart J* 10:995-1001 1935.

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was no leukocytosis. We have not heard anything about that before, it is slightly against rheumatic disease. The case was clearly being regarded as one of possible tuberculosis, because the sputum was examined repeatedly. The specimens were negative for acid-fast bacilli, and that is the rule in tuberculous pericarditis. Fluid was obtained from the pericardium, but unfortunately we are told nothing about it. I think we can assume that it was not a septic fluid. The patient got worse following the dry taps, was admitted to this hospital and perished within a few hours.

My diagnosis is tuberculous pericarditis. I think that it was acute, but possibly there had been some older element, because of the calcifications in the x-ray films. He probably had tuberculosis of the lung to account for the bloody sputum toward the end of his existence. He may have had tuberculoma of the brain, although there is only the very slightest indication for it. He probably died of terminal miliary spread, because that is the usual course in most cases. You will note that there is no definite evidence for that diagnosis. It is simply suggested because most cases of pericarditis that I have seen occurring in young adults and children with no other evidence of rheumatic disease, with no other evidence of involvement of anything else but the pericardium, with no etiologic factor discernible from examination of the fluid and with a duration of four months or more, have usually turned out to be tuberculous.

DR TRACY B. MALLORY: Would you like to give your impression, Dr. Williams?

DR CONGER WILLIAMS: At the time of admission our problem was treatment of the emergency. The patient was actually in a state of shock. No pulse was perceptible. He was deeply cyanotic, especially in the legs and hands. Of course our first consideration was cardiac tamponade to explain this picture, but one thing that bothered me about that diagnosis was the absence of marked distention of the neck veins. Dr. DuToit suggested that perhaps the absence of distended neck veins could be explained by diminished cardiac output. We also considered the possibility of an advanced rheumatic myocarditis with peripheral vascular collapse, because of the previous story of murmurs. Nevertheless, we thought there was an excellent chance that this man had pericardial tamponade and should, therefore, be tapped. This operation was performed by Dr. Soutter. He was unable to get any fluid from the pericardium. The patient died soon afterward.

DR PAUL I. WHITE: May I ask if there is certainty that the calcification is in the pericardium or in the heart and not elsewhere?

DR TOUFIC H. KALIL: Not without fluoroscopy. These films were done on the outside, and a lateral film was not taken. That may well be behind the heart.

DR WHITE: I should like to point out that it is possible to have both pericarditis of a chronic constrictive nature, possibly tuberculous in origin, and rheumatic heart disease in the same case. We have seen such cases but they are few and far between and apparently coincidental.

Dr. Pickering has looked up and seen quite a few cases of tuberculous pericarditis, and I should like to ask him whether the heart is enlarged in those cases and whether the subjacent or subpericardial myocarditis is diffuse enough to give the picture of an enlarged heart and to produce murmurs with no specific changes in the electrocardiogram. Of course the changes often found in the electrocardiograms in such cases are in part due to the subpericardial myocarditis, but perhaps there is more than that. In our chronic constrictive pericarditis cases there was cardiac enlargement in something over half. It seems as if the myocardium, as well as the pericardium, was involved.

DR PICKERING: I am not sure that I can answer that. I am certain that the myocardium is abnormal. At any rate, by the time the fluid is absorbed in tuberculous pericarditis it certainly behaves like that, in the sense that it does not respond in the ordinary way to changes in venous pressure, and my "pathologist friends" tell me that the myocardium looks abnormal. Nor am I able to answer the question regarding the heart size. We really see so few of these that we only get definite evidence about the size of the heart if we replace the fluid with air or if the patient is examined post mortem.

DR EDWARD F. BLAND: Would Dr. Pickering accept the migrating pleuritis, in addition to the pericarditis, as favoring an acid-fast background?

DR PICKERING: If you can accept this as an inflammatory pleural effusion, certainly. The difficulty is, I suspect, that you have throughout this case a congestion arising from pericardial tamponade or changes in the pericardial cavity, and it is difficult, I think, without seeing the patient and personally examining him from all these angles, to come to this conclusion. I think the explanation is correct but would not like to bank on it at the present time.

#### CLINICAL DIAGNOSIS

Rheumatic myocarditis  
Cardiac tamponade?

#### DR PICKERING'S DIAGNOSIS

Tuberculous pericarditis, probably acute on a more chronic background and probably accompanied by pulmonary tuberculosis and possibly a terminal miliary spread.

#### ANATOMICAL DIAGNOSES

*Acute and chronic tuberculous pericarditis*  
Tuberculosis of lung and bronchial and mesenteric lymph nodes

## PATHOLOGICAL DISCUSSION

DR MALLORY Post-mortem examination showed a pericardium 5 to 10 mm in thickness, the thickening being due almost entirely to fibrosis, although there were a few spots with slight calcification of the pericardial sac. Approximately half the pericardial cavity was obliterated. There was a pericardial space left in two pockets amounting to a third or a half of the original sac. In that, we found just a few cubic centimeters of blood-stained fluid that did not seem to be enough fluid to consider that he had cardiac tamponade. The heart itself was very small, the heart and pericardium together weighed 450 gm. We have not separated the heart from the pericardium, but I doubt very much if the heart weighed over 275 gm. it might even be 250 gm. The valves were entirely normal. We found a number of large caseous bronchial lymph nodes, one caseous node in the mesenteric area and one small focus of active tuberculosis in the lung but no general miliary process. Sections from the pericardium and epicardium showed extremely marked fibrous thickening and inflammatory changes, and just beneath the epicardium in one spot a rather characteristic single miliary tubercle. I think we have enough to confirm the diagnosis of tuberculous pericarditis beyond a doubt.

Addendum by Dr Pickering I find this case of peculiar interest. A week previously I had communicated in the Ether Dome the results of work by Dr T Holmes Sellors, Dr G W S Andrews and myself, which had led us to conclude that, in Great Britain at least, most cases of constrictive pericarditis are of tuberculous origin. Briefly we observed the following: that out of 16 cases of tuberculous pericarditis observed over periods up to six years, 14 developed signs of constrictive pericarditis, 1 presented a persistent effusion and in only 1 was there no residual sign of pericardial disease, that acute tuberculous pericarditis unassociated with tuberculous pleurisy or ascites may give rise to relatively little subjective disturbance, and that the only 2 of our 7 patients with septic pericarditis who recovered from the acute stage presented no signs of constrictive pericarditis clinically or radiologically during the next four years. Calcification of the pericardium is common in constrictive pericarditis, this is the first case known to me personally in which post-mortem examination has revealed clearly both pericardial calcification and tuberculous pericarditis. It therefore adds weight to my belief that tuberculous is a common, and I think by far the most frequent, cause of constrictive pericarditis.

## CASE 33392

## PRESENTATION OF CASE

*First admission.* A fifty-one-year-old woman entered the hospital complaining of epigastric pain, nausea and vomiting of five months duration. The

pain was not related to meals and not relieved by food. Tarry stools had occasionally been noted. Fifteen years before admission a posterior gastroenterostomy for ulcer and a cholecystectomy had been performed. From this time until six months before entry the patient had been relatively free of ulcer symptoms.

Physical examination was essentially negative.

Examination of the blood revealed a red-cell count of 4,200,000, with a hemoglobin of 60 per cent, and a white-cell count of 8000. The urine was clear, but the sediment contained numerous red cells. Subsequently, four other examinations of the urine were negative. The stools were guaiac negative on three occasions. The gastric acidity was normal.

A gastrointestinal series showed no active ulcer. The left kidney appeared enlarged. Intravenous and retrograde pyelograms showed a mass in the upper left kidney. An x-ray film of the chest was normal. The patient was transferred to the Urological Service, where the left kidney was removed through a lumbar incision. The upper pole of the kidney was occupied by a 8.0-cm by 5.5-cm renal-cell tumor (hypernephroma), which had not broken through the kidney capsule.

*Second admission (thirteen years later).* The patient was asymptomatic until three months before admission, when grossly bloody bowel movements had appeared. At other times the stools were black. For two months she had been weak and tired, with some pain in the left lower quadrant. She sometimes felt a lump in the left lower quadrant. The epigastric pain also recurred and was relieved by food. Three weeks before entry a barium enema at another hospital had shown a "bowel tumor."

Physical examination revealed tenderness in the left lower quadrant, which prevented deep palpation. No mass was felt.

The urine was normal, as were the nonprotein nitrogen, serum protein and prothrombin time. The hemoglobin level was 12.4 gm.

Examination of the x-ray films brought in by the patient showed a shadow the size of a kidney in the left upper portion of the abdomen. A barium enema disclosed a persistent filling defect in the descending colon that had the appearance of a polypoid neoplasm (Fig 1). There was no obstruction to the passage of barium. The bones were normal.

On the fifth hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR LAURENCE L. ROBBINS In summary, this sixty-four-year-old woman had been complaining of bloody bowel movements for three months. There were associated symptoms of weakness, dizziness and left-lower-quadrant pain, with an abdominal mass at one time or another. At thirty-six years of age a gastroenterostomy and cholecystectomy

had been performed, and at fifty-one a hypernephroma of the left kidney had been removed

The first point that we can be sure of, in looking at this x-ray film, is that a barium enema had been given, and I should say that the patient was not particularly well prepared. There is a shadow extending well beyond the bowel, it apparently lies in close contact with the descending colon. Extending into the lumen of the descending colon is a small

There is, in addition, another shadow—a rather well defined mass—in the region where the left kidney is usually located

I should like to take this opportunity to point out the fact that frequently after nephrectomy a shadow is visible on the plain film of the abdomen that is perfectly consistent with a normal kidney shadow. That is probably what happened in the case under discussion. At least, I assume that the shadow is



FIGURE 1 Roentgenogram following a Barium Enema  
The upper arrows point to the shadow described as lying in the kidney bed. The lower arrows indicate the mass involving the descending colon.

lobular mass, which is perhaps better seen on this film. I do not know whether this is a postevacuation study or not, but gas, which is not seen in this first film, is present and the film probably represents a double-contrast enema after the injection of air. Here again we see the mass. Most of my discussion will hinge on whether this shadow beyond the confines of the bowel and this one protruding into the lumen of the bowel are parts of the same lesion

due to organized blood clot or fibrous tissue that remained after operation. But the fact that there is a shadow in that area does not mean that the kidney was not removed and that another abnormality was present.

DR. BENJAMIN CASTLEMAN: How long does this shadow remain?

DR. ROBBINS: For years. I cannot be certain because there is no plain film, but I think that this

particular shadow corresponds to the persistent postoperative one frequently seen

To go back to the lower shadow protruding into the descending colon, could this have been tied up with some inflammatory process such as a stromal ulcer with abscess formation and perforation into the colon? It seems unlikely from the data in the history. Likewise, I do not believe that other inflammatory processes, such as hyperplastic tuberculosis and amebic granuloma, need be considered. An infected diverticulum could give this appearance, but there is slightly more lobulation and more protrusion into the lumen than one would expect in diverticulitis. Also, there is no other evidence of diverticulum that can be seen on these films. One should consider a foreign body as a possibility, but that again seems unlikely. Endometriosis can produce a shadow similar to this, but it is somewhat higher than is usually found and, at the age of this patient, endometriosis is improbable. Furthermore, endometriosis would not account for the melena.

So far as tumor is concerned, the first thing to consider is whether this was an adenomatous polyp, which immediately means cancer until proved otherwise. Or was this extrinsic shadow a secondary tumor that extended from a primary cancer in the bowel? That is not impossible, although it is extremely unusual, from the x-ray standpoint, to see a sharply circumscribed mass of nodes adjacent to the tumor. This is much too smooth for the ordinary mass of lymph nodes, so that I am inclined to rule out the possibility of a primary carcinoma.

Could this have been metastasis or extension from the hypernephroma? The mass was somewhat lower than the area in which the descending colon was in contact with the kidney bed, metastasis would not be impossible, however, and it is difficult to be certain of the observation from the number of films at hand. I shall take the chance that the mass involving the bowel was entirely intraperitoneal, because if this mass arose from the kidney area and extended to the bowel, I think that the shadow of the psoas muscle would have been lost in that area where the mass overlies it, and the shadow of the psoas muscle is present. I cannot exclude metastasis from hypernephroma, but I have not seen cases in which the bowel was involved.

Certainly, we must consider the possibility of lymphoma. Here, again, unless it arose from the nodes in the mesentery or the mesocolon and extended into the bowel, this appearance is atypical. It could have arisen from the small bowel, but there is nothing in the history or the x-ray films to indicate small-bowel disease. Finally, it is somewhat more of a polypoid lesion than the usual lymphomatous involvement of the bowel.

Tumors of connective-tissue or smooth-muscle origin certainly cannot be completely excluded. The mass is relatively smooth and appears to be intra-

mural and to involve the mucosa. These tumors are prone to bleed rather profusely, as this one did.

There is another tumor that should be considered purely from what is seen on these films—that is, a carcinoid. Often the bulk of the tumor lies outside the bowel wall, producing in many cases a fairly sharply circumscribed mass that may be smooth. By and large, however, the lesions do not involve the mucosa, and there is no bleeding in the cases with which I am familiar. Also, the history in this case was too short, because a carcinoid usually is a slowly growing tumor. I have never seen one in this location in the bowel.

Actually, this is as far as I have a right to go. All I can say is that there was a tumor that involved the mucosa and a large mass extrinsic to the bowel. If this problem could be studied from spot films, even though fluoroscopy was excluded, there would be more opportunity of determining what this mass was.

From now on whatever I say is pure guesswork. I believe that there are three things to be considered primarily: extension from a hypernephroma, tumor of connective-tissue or smooth-muscle origin and carcinoid. I do not believe that we need to consider a primary carcinoma or lymphoma seriously. I believe that the most probable diagnosis is a tumor of connective-tissue or smooth-muscle origin.

DR FLETCHER H. COLBY: I wonder why a chest film had not been taken. The lung is the favorite site for hypernephromas to metastasize.

DR CASTLEMAN: Chest films taken in the Follow-Up Clinic in the Out Patient Department three years previously were negative. The patient had not been seen since that time.

DR WILLIAM CLARK: Has recurrence of hypernephroma been recorded in that long an interval?

DR ROBBINS: Yes.

#### CLINICAL DIAGNOSIS

Tumor of descending colon

#### DR ROBBINS'S DIAGNOSIS

Spindle-cell tumor of descending colon

#### ANATOMICAL DIAGNOSES

*Leiomyoma of descending colon*

*Pecurrent renal-cell carcinoma, with invasion of adrenal gland*

#### PATHOLOGICAL DISCUSSION

DR CASTLEMAN: Fairly extensive adhesions were found throughout the left side of the abdomen. The left colon, which contained a mass the size of a baseball, was freed laterally, and another mass was felt slightly higher in the left gutter. At first it was believed that this second mass was located in the pancreas, but on further dissection it proved to be in the adrenal gland. The entire mass was removed.

Grossly, it measured 9 by 5 by 3 cm (Fig 2 and 3), and microscopically it proved to be renal-cell carcinoma involving the adrenal gland

The colon was then resected The intraluminal portion of the intestinal tumor was relatively small,

sent merely the site of the previous nephrectomy, was the recurrence of the hypernephroma

A PHYSICIAN. Do you think that there was a metastasis to the adrenal gland?

DR CASTLEMAN I favor a recurrence with extension into the adrenal gland rather than a metastasis There was still some normal-appearing adrenal tissue on one surface of the tumor

DR WILLIAM BECKMAN How do you explain the bleeding?



FIGURE 2 Photograph Showing the Two Tumors That on the left is a section of the descending colon, with the intraluminal portion of the tumor That on the right is the left adrenal gland, with enlargement due to recurrent renal-cell carcinoma

measuring only 2 cm in diameter, it was covered with mucosa but was somewhat hemorrhagic (Fig 2) The extraluminal portion was much larger, 6 cm in diameter, and when sectioned it bulged exactly as a fibroid of the uterus bulged (Fig 3) This bulging is due to the tumor is held under marked tension capsule and that when the capsule is cut, emerges Microscopically, this tumor proved a leiomyoma Dr Robbins was therefore in his analysis of the shadow involving The upper shadow, which he considered



FIGURE 3 Photograph Showing the Cut Surfaces of the Two Tumors That on the left is the cut surface of the descending colon, note the bulging of the cut surface of the adrenal gland From the left the mucosa That is the surface of the stomach not have have h

# The New England Journal of Medicine

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## ROBERT NASON NYE

AGAIN, within a short space of time, the *New England Journal of Medicine* announces with sorrow the passing of a leader Dr Robert Nason Nye, its managing editor since 1937, succumbed on September 10 to an illness that, insidious in its onset and inevitable in its conclusion, was mercifully brief.

Dr Nye assumed the editorship of the *Journal* in 1937 on the retirement of Dr Walter Prentice Bowers, whose death a few weeks ago was recorded on this page. Where Dr Bowers left off Dr Nye began his own task, and gave to the *Journal* a skilled and devoted guidance that has brought it to a leading position among the medical periodicals of the world.

There are certain characteristics that distinguished Dr Nye from lesser individuals—his robust personality, his clear understanding, his intellectual integrity. He never compromised with his conscience. In the shock of his loss we realize that we shall not soon find one to take his place.

## TOXICITY OF STREPTOMYCIN

FROM the reports of its clinical use to date<sup>1, 2</sup> it is apparent that streptomycin will remain the treatment of choice in many infections due to gram-negative bacilli and to *Mycobacterium tuberculosis* until a better agent is found to replace it. The major drawbacks to its more widespread use, aside from its high cost, are the frequency with which development of bacterial resistance appears during its administration and the toxic effects that it produces, particularly when it is used in large doses or over long periods. Some reports dealing particularly with the otic complications of streptomycin have already appeared.<sup>3, 4</sup> Detailed observations of the toxic effects of this agent in a small group of patients who were treated for tuberculosis over long periods at the New York Hospital are particularly worthy of comment.<sup>5</sup>

The patients received 3 gm daily in eight intramuscular doses of 375 mg each of an almost pure streptomycin salt. The levels of streptomycin in the serum ranged between 7 and 30 microgm per cubic centimeter at the end of the three-hour interval between injections. It was considered advisable to interrupt treatment because of toxic manifestations in only 2 patients, both had an anaphylactic type of reaction, and in each case it was possible to resume treatment later.

There was remarkably little irritation at the site of the intramuscular injections in spite of their large number and frequency. Repeated intrathecal injections of 0.1 gm in 10 cc of isotonic salt solution were also well tolerated. There was usually a moderate pleocytosis from these injections in patients who had no evidence of central nervous-system disease, and occasionally there was headache, nausea and vomiting or some pain in the legs, the latter presumably due to transient irritation of nerve

roots Amounts of 0.2 to 0.375 gm intrathecally, however, produced untoward reactions, particularly after such doses had been given repeatedly for several weeks. In such cases there was somnolence, slowing of the respiratory rate and retention of urine. These symptoms usually lasted twelve to twenty-four hours and then disappeared. There were no sensory changes or persistent sphincteric disorders. Nystagmus was occasionally noted immediately after the intrathecal injection. Appreciable concentrations (4.5 to 17 units per cc) of streptomycin were always present in the cerebrospinal fluid forty-eight hours after the intrathecal injection of these large doses.

Symptoms of vestibular dysfunction of variable severity appeared uniformly between the seventeenth and the twenty-fifth day of treatment. Complete symptomatic recovery eventually occurred in all subjects. This recovery was presumably a result of activation of compensatory mechanisms rather than of restoration of labyrinthine function.

Deafness developed in 2 of 16 patients treated for four months, and in 3 others subsequently treated with the same preparations of streptomycin. Bilateral nerve deafness, amounting to from 50 to 100 per cent, occurred in 7 of the first 100 patients treated with streptomycin at the New York Hospital.<sup>6</sup> No tinnitus or impairment of hearing during or subsequent to the streptomycin treatment was observed in any of the other subjects, and no other neurologic disturbances were discovered in these patients. Five of the 7 patients with deafness had undergone prolonged intrathecal administration of streptomycin, and the other 2 had marked renal insufficiency, suggesting that the concentration of streptomycin in the central nervous system may be an important factor in the occurrence of deafness. Preliminary studies suggest that the site of this toxic reaction is the brain and that it is associated with liquefaction necrosis of the ventral cochlear and inferior vestibular nuclei.<sup>7</sup> Since these patients may also have had central-nervous-system lesions, the part played by such lesions, at least in the deafness, cannot be ruled out.

The vestibular disturbance accompanying streptomycin therapy is a most unusual complication of drug therapy. Farrington et al.<sup>5</sup> describe this disturbance as follows:

This reaction is characterized by the appearance of a mild headache, which disappears within twenty-four hours and is followed by the development of symptoms which resemble vertigo. The sensations differ from vertigo in that they seem to occur in a linear rather than a circular plane. At the completion of a sudden movement, such as reaching for an object, sitting up or leaning to one side, the afflicted person feels as though the movement was continuing in the same direction in which it had been going. Thus he experiences the sensation either of past pointing or of falling in the direction of the previous movement. Occasionally, a momentary delay in focusing the eyes after a sudden change in position will be noted. At the height of the reaction one patient displayed striking pendulum movements, similar to those observed in labyrinthectomized animals. When he assumed the erect sitting position suddenly, he swayed back and forth rhythmically for approximately sixty seconds.

There was a considerable variation in the intensity of the vestibular dysfunction experienced by the different subjects. At the peak of the reaction these subjects [the ones with moderate or severe involvement] were unable to sit up in bed unassisted and with the slightest motion were acutely uncomfortable even when lying flat. They were frequently nauseated, and occasionally they vomited. The symptoms usually persisted in an acute form for seven to ten days and then subsided almost entirely. The disappearance of the acute symptoms occurred with striking rapidity, sometimes within a period of twenty-four hours. In no instance, however, did complete recovery occur with the subsidence of the acute symptoms. Instead, the subjects entered into a phase in which the symptom was absent during ordinary activity but could be evoked momentarily by an unusual stimulus, such as an abrupt shaking of the head.

In general the stage of latent vestibular dysfunction persisted for approximately sixty days and then disappeared. During the fourth month of therapy all subjects except one were completely free from these symptoms while reclining or sitting erect in bed. Ataxia was absent as long as these persons could orient themselves visually with any fixed object. A staggering gait was present, however, when they attempted to walk in the dark or with closed eyes. In these particular instances the symptom has not been disabling and has slowly diminished in intensity during the nine months since the cessation of therapy. In no instance was streptomycin therapy interrupted because of vestibular dysfunction.

Nystagmus was seldom encountered. Only one patient manifested a sustained nystagmus, although in several other subjects fleeting nystagmoid movements of questionable significance were observed. In [another] patient a rotary nystagmus was observed.

The renal complications, although not severe and probably of no great significance, are nevertheless of some interest. A few patients showed transient reduction in renal function associated with nitrogen retention. Casts of various types appeared intermittently in the urine in the majority of cases; they were present when a highly acid urine was excreted and usually disappeared when the urine was alkaline.

Sensitization reactions were encountered oftener during treatment with streptomycin than with sulfonamides or penicillin. They were manifested chiefly by fever, dermatitis and eosinophilia. The last was either intermittent or sustained, ranged from 5 to 39 per cent and was noted in the great majority of the cases.

McDermott<sup>6</sup> also studied patients treated with impure lots of streptomycin. From a comparison of the reactions in such cases with those observed in patients treated with pure streptomycin it was concluded that the histamine-like reactions, irritations at the sites of injection and possibly sustained febrile reactions were not caused by streptomycin but by impurities, which are removable by refinements in the process of manufacture. All the other manifestations of toxicity that have been observed after the use of impure streptomycin have also occurred during the administration of the highly purified preparation of the drug.

From these observations, McDermott concluded that the immediate toxicity of highly purified streptomycin on long-continued administration is sufficiently low to justify the use of the drug in the treatment of serious and protracted infections, such as most forms of tuberculosis. Since streptomycin, however, can produce serious toxic reactions he believes that it is not advisable to use the drug in the treatment of benign infections with a generally favorable prognosis, such as minimal pulmonary tuberculosis and chronic brucellosis.

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one or another of the large metropolitan hospitals, accompanied by police escort and heralded by the wailing of sirens, are to be deplored. Physicians who, in their early years of training, were driven through city streets in a hospital ambulance appreciate the thrill of such a journey, not only to those in charge of the ambulance but also at times to the patient. And who does not pause, with a certain boyish thrill, to watch an ambulance go by? Ever so often, however, this excessive and, as a rule, unnecessary speed results in death or serious injury to the occupants or to innocent bystanders.

Racing over congested highways does shorten the trip to the hospital, but it is only occasionally that the minutes gained are of benefit to the patient, indeed, such a trip may be truly harmful to one who is seriously ill. Thus, a physician, when he learned that a patient with a compound fracture of the skull was being rushed to his hospital under police escort, sent out word through appropriate channels that the police escort was to slow the ambulance down to below thirty miles an hour, believing that this was better for the patient and all concerned. He then took pains to be sure that the necessary measures to ensure immediate treatment on arrival at the hospital were taken.

The matter has its entertaining side. Recently, a small patient who had swallowed a penny was being rushed to a metropolitan hospital. En route, the automobile was in collision with another, and five occupants of the cars were taken to a small local hospital because of minor injuries. On arrival at the hospital the penny was found on the floor of the mercy car. Whether the shaking up of the ride or that of the accident was the effective therapy was not discovered. But neither, as a matter of fact, is recommended as a specific form of treatment in similar cases.

Certainly, a speed of eighty or even sixty miles an hour over roads, summer or winter, is difficult to justify except in extreme cases, and the attending publicity, even though no accident results, seems in poor taste. Such publicity should be minimized, and better still, the public should be made aware of the fact that, generally speaking, extreme speed is unnecessary and may be harmful to the patient and to others.

## "MERCY CARS"

THE accounts that appear in the daily press from time to time describing the record-breaking speed made by so-called 'mercy cars' on their way to



## A HUNDRED YEARS AGO

With the multiplication of hospitals, dispensaries and charities of all descriptions, and the onward and upward march of pure medical science, there have grown into notice, and favor, too, institutions for providing families with the necessities of life, when the strong arm on which a wife and children placed their whole dependence for daily bread, is weakened, and the willing heart is overcome with assaults of disease. There is an office in Tremont street, where by the payment of from four dollars seventy-five cents to nine dollars fifty cents a year, a man, from twenty-five to fifty-two years of age, may draw weekly from four to six dollars, when an invalid. Besides the great benefit to the insured, there would be no complaint by the physician of poor practice by loss of bills, were the custom a general one, as it should be, of being fully insured. A scheme so admirable as this, and withal so strictly economical, addresses itself at once to the understanding, and we hope, therefore, that the benefits of that excellent institution, the Massachusetts Health Insurance Company, may be appreciated by the intelligent people of New England — Mr L M S, while engaged in his usual avocations, was attacked with severe pains in his bowels, and nausea, at noon. He was obliged to leave his business and return home. The pain was in the right hypogastric region, not constant, but intermitting, like colic pain. He took a cathartic, which was retained in the stomach three hours and a half, and was then vomited, without having any effect on the bowels. An enema was ordered, which moved the bowels freely, with much relief. In two or three hours after the enema, the spasmodic pain returned in the same spot on the right side, shooting through to the back. It became necessary to resort to opiates every few hours to relieve pain. He continued to vomit frequently, at first dark mucus and such drinks as he had taken, and finally vomitus colored by particles of dark blood. His pulse became more rapid and less distinct, his skin moist and cool. He continued to fail until he breathed his last. An autopsy was made by Dr J B S Jackson. The caecum and ileum were highly inflamed, but the cause of the inflammation was not discovered till the caecum was dissected from its bed in the iliac fossa, the appendix then was found closely adherent to the caecum, in an ulcerated and gangrenous condition. Within the appendix were two small masses of fecal matter in a hardened condition, these had ulcerated completely through the coat of the appendix. How long the appendix had been in this unnatural condition, it is impossible to say. It was probably of long standing, but not congenital. He had for the last three

or four years complained of pain and lameness in that region when more than usually fatigued, as to the length of time the fecal matter had been retained, no definite opinion can be given — Readers will doubtless recollect that a variety of comments appeared in this Journal on the dinner served up for the Massachusetts Medical Society. At the last anniversary it is believed the dinner proved quite satisfactory. It seems, however, that something more is wanted to give a gusto to the festivities of the occasion. A gentleman declares that a band of music is the one thing needful to give life to a very dull meeting. The mere act of eating oyster pie and fried cabbage is not sufficiently animating to stir up the enthusiasm of four hundred physicians. So next year he votes for music — Dysenteric affections are very general as they always are at the season of the coming in of new fruits, yet the number of deaths has been comparatively small, which gives reason to suppose that physicians, when seasonably consulted, have been successful in their prescriptions — Otis Clapp, of Boston, has in press a "New Manual of Veterinary Medicine on the Homeopathic Treatment of the Horse, the Ox, the Sheep and the Dog and other Domestic Animals," by F A Gunther. Translated from the third German edition, with considerable additions. Surely this is an exhibition of folly, remarkable even in imaginary science — John U Haezer, of Sullivan Co, Tenn, aged 114, walked recently, half a mile to vote! He has voted at every presidential election that has been held in the United States — The American Geological Society was in session in Boston last week at the Marlboro' Chapel. There was a strong representation of the science of the country present. It was noticeable that quite a number, if not a majority of the Society hailed from the medical profession. The true way of keeping up an interest in any branch of natural science is to bring those together frequently who are devoted to such pursuits. It is only by common labors and freely interchanging thoughts, that progress can be made in elevated branches of knowledge — An eminent physician of New Orleans was called recently, it is said, to Madame A, 1 of a slight fever. He wrote a prescription, the directions of which were followed strictly, and a short time only after the medicine for Madame A was taken, she expired. It subsequently appeared that he had ordered *morphine* instead of *quinine*. The error, which is only explained by the distraction arising from the pressure of professional engagements, is irreparable — Extracted from the *Boston Medical and Surgical Journal* August-September 1847

## WALTER PRENTICE BOWERS

1855-1947

Walter Prentice Bowers was born in Clinton, Massachusetts, on May 19, 1855, one of the eight children of the Reverend Charles Manning and Ella (Damon) Bowers. At the time of his birth his father's yearly salary as minister of the First Baptist Church was five hundred dollars. At no time did it permit any unusual expenditures on the education of so large a family, and the three years after Walter's graduation from high school found him working in a drugstore, earning the money to put himself through Harvard Medical School.

He matriculated in the school in 1876 and graduated with honors in 1879. After serving for a time in the Out Patient Department of the Massachusetts General Hospital, he joined the staff of the Worcester Lunatic Hospital, now the Worcester State Hospital and settled in Lancaster to practice. Ill health forced him to resign from this post in 1881, and he moved to Clinton, where he established the practice that was to occupy him continuously until his death. In 1880 he married Helen M. Burdett, of Clinton, whom he survived. They had no children.

Dr. Bowers was in every way a leading citizen of his community. He founded the Clinton Hospital in 1889 and was president of its association for fifty years, even in the past year he had led the successful campaign to raise funds for its new building. He had been a member of the Board of Selectmen, town-meeting moderator, a member of the Board of Health, vice-president of the Clinton Trust Company and a director of the Clinton Savings Bank.

In 1894 he became a member of the Massachusetts Board of Registration in Medicine, and in 1913 its secretary. He had been a counselor of the Massachusetts Medical Society since 1898 and was president from 1912 to 1914. He was presi-

dent of the Worcester District Medical Society in 1903.

In 1920 Dr. Bowers was active in effecting the purchase by the Society of the *Boston Medical and Surgical Journal*, then in an honorable but impecunious decline. He became its managing editor in the following year, thus assuming an added responsibility that necessitated his retirement from the secretaryship of the Board of Registration in 1922,

a year before he would have been eligible for a pension. During his editorship, which he held until 1937, he brought the *Journal* back to a position of national prominence, fully justifying its purchase by the Society.

We all knew Dr. Bowers as an uncompromising advocate of the best type of medical practice, as a tireless worker in behalf of the Massachusetts Medical Society and as a leading medical journalist. His community knew him as a public-spirited citizen and as a skillful, devoted practitioner of medicine. A smaller circle knew him

as an ardent sportsman, carrying his fishing rod with him in the spring and his gun in the fall on his long drives through his native countryside, and as the hunting companion of his old friend, the late Dr. E. Amory Codman. A few only knew of his hidden kindnesses, of the young people whom he had helped through school or college or of the aid that he had given to various younger colleagues in his profession.

In the whole conduct of his life he was the good physician, and it was as such that President Conant of Harvard University recognized him in conferring on him the honorary degree of master of arts in 1935, shortly after Dr. Bowers's eightieth birthday. — "A physician devoted to his calling, for more than forty years a general practitioner in Worcester County, he has brought skill and wisdom to countless homes."



## CORRESPONDENCE

## INSTITUTE OF THE HISTORY OF MEDICINE

To the Editor An editorial that appeared in the May 22, 1947, issue of the *Journal* suggests for discussion several topics that are of great interest to the medical profession of Boston and New England. The title of the editorial is "New York Academy of Medicine," and the writer points out some of the activities of the New York institution, briefly compares Boston with New York and closes with a paragraph that I quote in full, underlining three words to which I wish to call attention

There is, *curiously*, no similar organization in New England, although the various functions of an academy are *adequately* carried on by the state medical societies, the medical schools and, notably, the Boston Medical Library, fellowship in which carries with it a dignity and an intellectual prestige that still have their value

"The various functions of an academy are *adequately* carried on by *notably* the Boston Medical Library." As I understood the situation, the basis for the appeal by the Boston Medical Library to the Massachusetts Medical Society for assistance was that the services actually rendered by the Library were notably inadequate

I quote from the Fleming report *A Factual Survey of the Medical Libraries in Boston*, dated 1941 but still pertinent, since little if any progress was made during the War. The first quotation is from the general section of this survey

The administration of Boston's medical libraries has not attained the general standards of library administration in evidence in the rest of the country. It is noticeable that the use made of Boston medical libraries has been generally less than that commonly reported elsewhere. Although many factors enter into this apparent difference in use, it is the opinion of this observer that the basic factors are the failure of the Boston medical libraries to provide (1) adequate reading facilities, (2) expert bibliographical and reference services, (3) instruction in the use of the library, (4) ready access to the literature, (5) messenger service between library and laboratory and (6) sufficient copies of heavily used material

Persons who use the Boston Medical Library may easily check on these points to see what is true of that institution

I quote also from the section of the report dealing with the Boston Medical Library.

Despite the magnificent resources which it has available, neither the support nor the use of the library has been up to expectations. (Some of the alleged trends are then noted.) If these assumptions are true, then support for the Boston Medical Library will continue to fall off, and this splendid collection, which is unexcelled in many fields and vitally essential for the practicing physician and research worker alike, will face a somewhat uncertain future. This library is now faced with the serious problem of adjusting itself to new conditions. Should it remain the "gentleman's" library of the past, where tradition still is the important factor, or should it expand its services to meet the changing conditions which confront it

The rather restrained Fleming report does not use the words "adequately" and "notably" to characterize the way in which the Boston Medical Library is carrying on its functions

The writer of the editorial says, "There is, *curiously*, no similar organization in New England," but he does not satisfy the curiosity of the medical profession whom he is addressing. There have been, to my knowledge, in the past thirty-five years, two serious and not insignificant movements to improve greatly what may be called briefly the general set-up involving the Boston Medical Library as the center. These came to nothing and local petty jealousies were a critical factor in preventing progress. The reason there is no such institution in New England is because there are not persons enough who care enough to do enough to create it.

Few persons who have given thought to the subject are satisfied with the situation as it exists. Not only is it confused and chaotic, but the wider and deeper implications that are involved receive almost no attention. Yet the "magnificent resources of the Boston Medical Library unexcelled in many fields," themselves a high tribute and a great memorial to the men in the past who loved books because "the chains of the mind are broken" by understanding of the past," lie there waiting for the magic touch of the historian to make them effective in leading us toward freedom

The most striking fact about the world today is the confusion, much of it due to the rapid rate of change. To make

adjustment to this new environment we need new ideas, new emphasis on and ways of using old ideas, new ways of escaping from old ideas that obstruct progress in our path toward freedom. Among the new ideas, which are sure to come, there will be many based on unrealistic thinking with the drive of emotional imbalance behind them. Some of these new ideas will be merely "old foes with a new face." They can be met, they must be met, with ideas based on realistic thinking, on a comprehensive and just evaluation of all the facts available, supported by sane and balanced emotional drives

Medicine cannot escape from the general confusion. It is at least a little off balance, owing chiefly to the dominance of the specialist, whose weakness is that he has lost perspective. This cannot be remedied by merely seeking the help of the general practitioner. What is needed is a reorientation of medicine itself in the light of the comprehensive view of the world, extensive and intensive, that is open before us today. How can we get a truer perspective?

"History," writes Lord Acton, "is a narrative told of ourselves, the record of a life which is our own, of efforts not yet abandoned to repose, of problems that still entangle the feet and vex the hearts of men. He adds, "History compels us to fasten on abiding issues and rescues us from the temporal and the transient."

It may be objected that the history of medicine is a brood reed on which to lean: it has but a small and relatively unimportant place in the medical curriculum and little part in university education today. The reply to this objection is that a different approach is needed. Do we find in the tradition of the English-speaking peoples that the writing of history has been the monopoly of university professors? We Gibbon and Grote and Macaulay and Lingard and Prescott and Motley and Bancroft and Lea, to name but a few, university schedules? Perhaps it would be well for the history of medicine to break away from university entanglements

In summary, there is opportunity in Boston for further development of the sources of history, including a central reference library for all kinds of books that have to do with the healing art in any of its branches. In the interest of economy and efficiency, co-operation is desirable in every practicable way among all institutions needing medical libraries. Medical schools, hospitals and other institutions might reduce their libraries to the minimum compatible with the immediate working needs of the institution. Books not needed for the working library could be deposited in the central library. Facilities for the transportation of books are generally regarded as necessary

A critical need is that there be developed in the central library a division of research, under the direction of a professional historian expert in research and exposition. As an integral part of the organization and so endowed that research does not have to be stopped because an additional janitor is needed, such a department has great possibilities. It might be called the Institute of the History of Medicine if that seemed desirable. Bibliographic services are usually rendered by well equipped libraries. In an important sense, research should be the mainspring of the activities of the library and should be carried on at all times

There are needed adequate reading rooms and work rooms, large and small, and ample space and other facilities for medical activities now carried on in the Boston Medical Library, such as those of the Massachusetts Medical Society and its *New England Journal of Medicine*. Perhaps others would be added later. It is clear that the present buildings of the Boston Medical Library do not lend themselves to the development of a large auditorium and rooms appropriate for smaller meetings

What the project is called is of secondary importance. It might be planned to meet the present, and so far as can be foreseen, the future needs of the community, which include New England, for years to come. In any case it should be an outgrowth of community conditions to meet community needs, keeping in mind always the principle of seeing the part in the light of the whole. If this principle is followed, the project might become of national importance, worthy of support by educational philanthropy

STEPHEN RUSH

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Boston

## BOOK REVIEWS

*Victory over Pain. A history of anesthesia.* By Victor Robinson, M.D. 8, cloth 338 pp., with 17 illustrations and 10 plates. New York: Henry Schuman, 1946. \$3.50

Dr. Robinson has written a history in a popular narrative form of the means used for the relief of pain and the production of surgical anesthesia from the time of antiquity when the Greeks and Romans used herbs for this purpose, to the present, when local anesthesia in its various forms is prevalent and the possibilities of curare are being investigated.

Half the volume is devoted to the discovery and development of surgical anesthesia, by ether and nitrous oxide in the United States and by chloroform in England, during the period 1832-1850. The facts relating to Long, Wells, Jackson and Morton are given in an impartial manner and Dr. Robinson wisely refrains from taking sides in the controversy which is still alive after a century has passed since Samuel Colt gave his exhibitions with laughing gas. The quip of Oliver Wendell Holmes that the wisest verdict in the matter "To (c) either" is quoted as Dr. Robinson's judgment on the merits of the case.

Samuel Colt, of Hartford, Connecticut, inventor of the famous Colt revolver, gave exhibitions on the street corners in Ware, Massachusetts, in 1832, of the effects of laughing gas for the purpose of raising money to be used for expenses incidental to inventing his revolver. In the section on chloroform is related the story of Samuel Guthrie and the part he played in the discovery of chloroform coincidental with Sobbeiran and Liebig in 1831.

The first part of the book presents a short summary of the subject in the classical, medieval and renaissance periods and the seventeenth to the early nineteenth centuries with chapters on Humphry Davy and nitrous oxide, Henry Hill Hickman and carbon dioxide and Mesmer and mesmerism. The last part is devoted to local, regional and refrigeration anesthesia, twilight sleep and complicated modern anesthesia apparatus. The text concludes with a bibliography that is nothing more than a short reading list of books used by the author in writing his history.

The book is well published except that some of the illustrations are not up to standard quality and is recommended for medical-history collections.

*Therapeutic Exercise.* By F. H. Ewerhardt, M.D., and Gertrude F. Riddle, B.S. R.N., R.P.T. 8" cloth 152 pp. Philadelphia: Lea and Febiger, 1947. \$2.50

In the preface the authors state that the purpose of this manual is to provide a text for students training in physical education, occupational therapy and physical therapy. These three groups are intensely interested in the motions that the normally take place in the various joints of the body. The textbooks on which they depend to obtain this knowledge are as a rule of the type that deal with elementary anatomy and physiology. A comparatively small portion of these texts is devoted to motion. Some books discuss at length muscle action or body mechanics but such works are few and are not quite adequate. The appearance of this manual is therefore welcome.

It supplies information pertaining to joint motions it suggests the proper exercises to preserve such functions in health and to restore them when they become subnormal or absent after disease or injury. This is carried out in detail. For example nine pages and eleven drawings are devoted to instruction in the use of the goniometer to measure angles or degrees of motion. Fourteen pages present a brief review of the plexuses of nerves in the upper and lower extremities, of their normal functions, the causes, signs and symptoms of their abnormal status, the tests to be employed in the determination of the extent of their dysfunction and the methods used to restore them to normalcy. In addition to the treatment of the upper and lower extremities the book deals with abnormal conditions of the abdominal muscles and curvatures of the back, suggesting the proper remedial exercises.

Poliomyelitis and spastic diseases are each given an entire chapter that on the former deals at length with muscle function testing as well as muscle training whereas the latter discusses the medical, surgical and orthopedic aspects, together with exercise, vocational, recreational and physiotherapeutic measures for the restoration and co-ordination of the natural body mechanics.

Some of the valuable information scattered throughout the book could advantageously have been tabulated in one section serving as a source of ready reference. Thus, in the next edition the authors might consider the advisability of incorporating a table of the skeletal muscles, with their origins, insertions, nerve supplies and actions. Another omission comprises drawings, diagrams and cuts, their inclusion in coming editions will greatly add to the value of this book by making students visualize the body structures and their relations and functions.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Pyle's Surgical Handicraft. A manual of surgical manipulations: minor surgery and other matters connected with the work of surgical dressers, house surgeons and practitioners.* Edited by Hamilton Bailey, F.R.C.S. (Eng.), surgeon, Royal Northern Hospital, London; surgeon and urologist, County Hospital, Chatham; surgeon, Consolation Hospital, Lambeth; senior surgeon, St. Vincent's Clinic and Italian Hospital, and consulting surgeon, Metropolitan Ear, Nose and Throat Hospital, Porters Bar Hospital and Essex County Council. Fifteenth edition, fully revised. 8, cloth 668 pp. with 789 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$7.00.

This standard British manual, the joint work of forty four authors has been revised to bring it up to date since the publication of the previous edition in 1944. Technical procedures have been depleted pictorially necessitating the addition of a large number of illustrations. The popularity of the manual is evidenced by the editions printed since the publication of the first edition in 1884. The volume is well published in every way and is a credit to its British printer.

*A Manual of Otolaryngology, Rhinology and Laryngology.* By Howard Charles Ballenger, M.D., associate professor and acting chairman, Department of Otolaryngology, Northwestern University School of Medicine and surgeon, Department of Otolaryngology, Evanston Hospital, Evanston, Illinois. Third edition, enlarged and revised. 8" cloth 352 pp. with 135 illustrations and three color plates. Philadelphia: Lea and Febiger, 1947. \$4.50.

This standard manual has been revised by the addition of new material and a chapter on headaches and neuralgias of the face and head. Illustrations on clinical anatomy have been added to the various sections. The text has been prepared primarily for undergraduate medical students but should prove useful to general practitioners and nurses.

*Handbook of Medical Emergencies.* Compiled by eight physicians who recently completed their internships, headed by Thomas B. Fitzpatrick, M.D. 16" cloth 106 pp. Lithographed. Cambridge: Harvard University Press, 1947. \$2.50.

This pocket-size manual the combined work of a committee of eight young physicians and a board of twenty three eminent specialists in various fields of medicine presents in complete outline form for quick reference the essential differential diagnostic points and procedures and specific and practical management of over three hundred acute medical emergencies. Included are the exact dosages, routes of administration and complications met with during the use of the various therapeutic agents. There are general chapters on penicillin, sulfonamide and parenteral therapy. Then, in order, are discussed the infectious diseases, acute and chronic intoxications, diseases due to physical agents and diseases of the various systems of the body. The volume is concluded with tables of equivalents of weights and measures and of normal values in blood, urine and spinal fluid, a list of abbreviations and an index. It should prove especially useful in the wards of hospitals. The pretention of some rare conditions, such as metallic, food and drug poisonings should make it valuable to the general practitioner.

*Textbook of Medicine* Edited by Sir John Conybeare, K B E, M C, D M (Oxon), F R C P, physician to Guy's Hospital 8°, cloth, 1170 pp., with 30 plates and 25 figures Baltimore Williams and Wilkins Company, 1946 (Printed in Great Britain) \$8 00

First published in 1929, this standard British textbook, which is the joint effort of seventeen contributors, has been revised to include material accumulated since the publication of the last edition in 1945. The articles on malaria, black-water fever, bacillary dysentery and typhus have been largely rewritten. The article on heat has been rewritten and transferred to the section on tropical diseases. There is a new article on the menopause, and those on thyrotoxicosis and diseases of the pituitary body have been revised. A section on penicillin and an appendix on aviation medicine have been added.

*P-Q-R-S-T A guide to electrocardiogram interpretation* By Joseph E F Riseman, M D, associate in medicine, Harvard Medical School, instructor in medicine, Tufts College Medical School, and visiting physician, Beth Israel Hospital, Boston. Second edition. Oblong 16°, cloth, 84 pp., with 170 illustrations. New York Macmillan Company, 1947 \$3 50

This manual, first published in 1944, has been revised and reset.

*Peripheral Vascular Diseases (Angiology)* By Saul S Samuels, M D, consulting vascular surgeon, Long Beach Hospital, New York, attending vascular surgeon, Brooklyn Hospital for the Aged, and chief, Department of Peripheral Arterial Diseases, Stuyvesant Polyclinic Hospital, New York 8°, cloth, 85 pp., interleaved. New York Oxford University Press, 1947 \$2 50 (Oxford Medical Outline Series)

This outline of angiology should prove useful to students and physicians, since it furnishes in a compact form the essential facts necessary to an understanding of the various diseases of the peripheral vascular system. The material is well organized. The initial chapters deal with the anatomy of the blood vessels and the autonomic nervous system, classification and symptomatology and objective signs in general, followed by the various diseases — arteriosclerosis obliterans, thromboangitis obliterans, Raynaud's disease, embolism, varicose veins and the rarer conditions. Each disease is discussed from the viewpoints of etiology, pathology, symptomatology, objective findings and treatment. A selected list of references is attached to each chapter.

*Proceedings of the Eleventh Annual Convention of the National Gastroenterological Association* 8°, paper, 187 pp., with 23 illustrations. New York Medical Authors' Publishing Company, 1947 \$2 50. Reprinted from *Review of Gastroenterology*.

This reprint makes available in one small volume the various papers on peptic ulcer, infectious hepatitis, psychosomatic medicine and gall-bladder disease read at the convention, held in New York City June 19-21, 1946.

*Physiological and Psychological Factors in Sex Behavior* By S Bernard Wortis, M D, and others 8°, paper, 42 pp. New York New York Academy of Sciences, 1947 50 cents. Reprinted from *Annals of the New York Academy of Sciences* (Vol XLVII).

This pamphlet contains a series of five papers that were read by authorities in their fields at a conference held by the Section of Biology and the Section of Psychology of the Academy on March 1, 1946. The material is divided into two parts: animal behavior and human behavior. In the first part the animal endocrines in relation to sexual behavior and sex behavior in primates are discussed, and the knowledge to date summarized. These papers are documented with lists of pertinent references to the literature of the subject. In the second part normal and aberrant sex behavior and sex culture are considered. Alfred C Kinsey, discussing sex behavior in the human animal, bases his conclusions on an extensive case-history study that has been under way at Indiana University during the past eight years, and has accumulated to date over ten thousand histories obtained by first-hand interviews with persons of wide social range, of all ages and of a diversity of backgrounds. The evidence seems to point to the fact that sex practices heretofore con-

sidered abnormal are normal in the pattern of biologic behavior. The papers are well written, clear in expression and succinct. The pamphlet is well published in every way and should be in all medical and social libraries and in the private collections of all persons interested in the scientific aspects of sex behavior.

## NOTICES

### MASSACHUSETTS MEMORIAL HOSPITALS

The Massachusetts Memorial Hospitals have opened its their Outpatient Department on East Concord Street a Seizure Clinic to be held on Thursday afternoons at 2 o'clock. This clinic will be under the charge of Drs Bernard Bandler and Charles Kaufman, of the Department of Psychiatry, Boston University School of Medicine. Appointments for patients wishing to attend this clinic may be made by telephone to the clinic secretary, Miss Cutter, at KENmore 9200.

### AMERICAN ALLERGY FUND GRANTS-IN-AID FOR SCIENTIFIC RESEARCH

The American Allergy Fund, an organization for the advancement of medical science founded in Cleveland slightly more than a year ago, has announced that grants in aid for scientific research are available. The grants will be made to investigators in the biologic sciences, both medical and non-medical, whose problems meet the requirements of the Scientific Advisory Council, preference will be given to problems with immediate relation to allergy, although investigations in physiology, biochemistry, pharmacology, immunology, genetics and other basic sciences are solicited. Grants will be made for one year in amounts not to exceed \$3,500, and may be renewed from year to year if the work is progress warrants continuation.

Applications (seven copies) should be addressed to the American Allergy Fund, 525 Erie Building, Cleveland 15 Ohio (attention Scientific Council), and should contain the following information: a statement of specific research problems and an outline of the method or methods of procedure to be followed, a description of research facilities in the institution where the investigator will employ the grant, tentative budget, and a statement of the applicant's research record — accompanied, if possible, by publications or reprints.

## SOCIETY MEETINGS AND CONFERENCES

### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 2

FRIDAY, OCTOBER 3  
\*10 00 a m -12 00 m Medical Staff Rounds Peter Bent Brigham Hospital  
MONDAY, OCTOBER 6  
\*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital  
TUESDAY, OCTOBER 7  
\*12 15-1 15 p m Clinicorontgenological Conference Peter Bent Brigham Hospital  
WEDNESDAY, OCTOBER 8  
\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater Peter Bent Brigham Hospital  
\*Open to the medical profession

OCTOBER 3 AND 4 New York Academy of Sciences. Page 348 111  
of August 28  
OCTOBER 6-10 American Public Health Association. Page 456 111  
of March 20  
OCTOBER 6-17 New York Academy of Medicine. Page 348, issue of August 28  
OCTOBER 9 Practical Points in Geriatrics. Dr Roger I Lee. P. tucket Association of Physicians. 8 30 p m Haverhill  
OCTOBER-DECEMBER Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 14  
OCTOBER 13-18 Medical College Conference and Seminar for Pathology. Medical Examiners and Coroners. Page 242, issue of August 14  
OCTOBER 29-31 New England Postgraduate Assembly. Copley Pl. Hotel Boston  
NOVEMBER 13-15 Association of Military Surgeons. Annual Meeting. Hotel Statler, Boston  
FEBRUARY 6 American Board of Obstetrics and Gynecology. Page 2 issue of August 14  
APRIL 19-23 American College of Physicians. Page xii, issue of July 15  
MAY 6-8 American Association for the Study of Gout. Page xii, issue of July 31  
MAY 11-15 American Association on Mental Deficiency. Page 1 issue of July 24

(Notices continued on page 511)

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## A COMPARISON BETWEEN THE CLINICAL EFFECTS OF PYRIBENZAMINE AND THOSE OF BENADRYL\*

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NEW YORK CITY

ALTHOUGH twenty articles on the clinical effects of Benadryl have appeared in the American literature since early in 1946, when the drug was introduced, only five are to be found on Pyribenzamine. Feinberg and Friedlaender<sup>1</sup> are the only investigators who have made serious inquiry into the practical value of both drugs, and no statistics are available on the relative efficiency of these two agents in the same subject. Furthermore, their prophylactic and therapeutic possibilities in "constitutional" reactions to overdosage of allergenic extract have been examined in only 8 cases.<sup>2</sup> The purpose of the present report is to add observations on Pyribenzamine in 150 adult patients and on the practical use of Benadryl in 53, including cross-trials in 33 cases and the treatment of "constitutional" reactions with the histamine antagonists in 20.

### MATERIALS AND METHODS

A majority of the patients were inpatients or outpatients complaining of hay fever, bronchial asthma or acute (often drug) urticaria, whereas a few had atopic dermatitis, chronic urticaria, dermatographism or acute serum reaction. Sixteen patients who had developed hay fever, asthma or cutaneous allergy directly after an overdose of therapeutic allergen were given one of the two antihistaminic drugs orally on twenty such occasions to determine its value.

The dose routinely prescribed was 50 mg. by mouth, to be repeated in one to four hours if symptoms persisted or recurred but not oftener than five times in any twenty-four-hour period. Usually, one such dose sufficed to control the symptoms for four hours, so that few patients ingested more than two or three a day. The drugs were restricted to symptomatic relief and were never employed prophylactically.

Many of the trials were initiated under our direct supervision or that of assistants, so that the results might be judged objectively as well as subjectively.

### RESULTS

#### Clinical Effectiveness

**Constitutional reaction.** The disorder most susceptible to the drugs appeared to be the constitutional reaction that follows overdosage of allergic patients. If such responses were not of violent intensity, they almost invariably diminished or disappeared twenty or thirty minutes after the oral administration of 50 mg. of the histamine antagonist. The blanching of a brilliant erythema and the diminution of acute urticarial wheals were usually too rapid, once initiated, to resemble spontaneous resolution. Asthma was relatively refractory to the drugs as compared to nasal or cutaneous manifestations (Table I).

Twelve cases of mild systemic reaction were treated with Pyribenzamine. Three subjects who developed generalized erythema and slight wheezing lost the cutaneous signs and most of the bronchospasm twenty minutes after ingesting 50 mg. of the drug. Three others had similar manifestations, which were completely controlled. Another patient, with accidentally induced hay fever, showed complete recovery half an hour after the taking of a 50-mg. tablet, and a similar case was partially relieved. Pruritus of the eustachian tube and facial erythema that had followed an overdose yielded partially to a tablet of Pyribenzamine. The urticarial eruptions of 3 pollen-inoculated subjects responded spectacularly to the drug, and another patient required two hours for the clearing of the skin. Thus, there were complete responses in 8 and partial responses in 4 cases to a single 50-mg. dose of Pyribenzamine in 12 patients with constitutional reactions who received no other treatment (Table I).

The situation with accidentally induced asthma was less encouraging. When bronchospasm occurred

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shortly after an inoculation of allergenic extract and was of marked intensity, Pyribenzamine was without effect in 2 of 4 cases. Adrenalin, however, brought prompt relief.

The 4 cases of systemic reactions treated with Benadryl by mouth appeared to respond as well as those treated with Pyribenzamine.

*Acute urticaria* was next in order of susceptibility to the antihistaminic agents. There were 27 cases of acute drug allergy, 21 being referable to penicillin and 2 to sulfonamides. Four patients lost not only the subjective discomfort but also the lesions. Eighteen ceased to itch and showed diminished cutaneous signs. One case of phenobarbital and 1 of novocain hypersensitivity showed partial im-

In another group of 8 patients with nonseasonal allergic rhinitis similar tendencies to yield to the drugs were shown in 6 cases. The number of observations was obviously too small for definite conclusions. This paucity of sampling likewise applies to the remainder of the data, which are presented mainly to add to the still inadequate figures available in the literature.

*Other conditions.* Extrinsic asthma treated with the drugs showed improvement in 7 of 11 cases, and intrinsic asthma responded partially in 3 of 9 cases. Of the 20 cases in which observations on asthma of all types were made, 50 per cent yielded to drug therapy, but in most cases the improvement was

TABLE 1 *Comparative Results of Histamine Antagonists in Allergic Disorders*

DISORDER	RESULTS WITH PYRIBENZAMINE				RESULTS WITH BENADRYL			
	COMPLETE RELIEF	PARTIAL RELIEF	NO RELIEF	TOTAL PATIENTS RELIEVED	COMPLETE RELIEF	PARTIAL RELIEF	NO RELIEF	TOTAL PATIENTS RELIEVED
Allergic rhinitis								
Extrinsic seasonal (hay fever)	27	24	9	51 (85%)	14	17	7	31 (82%)
Extrinsic nonseasonal	3	1	2	4 (67%)	2	0	0	2 (100%)
Intrinsic	2	0	0	2 (100%)	0	0	0	0
Asthma								
Extrinsic seasonal	0	0	1	0	0	1	0	1 (100%)
Extrinsic nonseasonal	2	4	2	6 (75%)	0	0	1	0
Intrinsic	0	3	4	3 (43%)	0	0	2	0
Urticaria, acute								
Due to drug	4	20	3	24 (89%)	0	2	0	2 (100%)
Due to other factor	2	0	2	2 (50%)	0	0	0	0
Urticaria, chronic	3	3	6	6 (50%)	1	0	0	1 (100%)
Dermatitis, atopic	0	1	2	1 (33%)	0	0	2	0
Pruritus	0	1	1	1 (50%)	0	0	0	0
Constitutional reaction								
Mild	5	4	0	12 (100%)	2	1	0	3 (100%)
Moderately severe (asthma)	2	0	2	2 (50%)	0	1	0	1 (100%)
Dermographism	0	1	0	1 (100%)	0	0	0	0
Serum reaction	0	1	0	1 (100%)	0	0	0	0
Totals	53	63	34	116 (77%)	19	22	12	41 (77%)

provement, whereas a streptomycin rash and an exfoliative dermatitis due to gold therapy resisted all antihistamine therapy. Acute urticarial eruptions of unknown etiology in 2 of 4 cases responded spectacularly.

Successful attempts were made to control acute urticaria with Benadryl in 2 cases. Chronic urticaria yielded to treatment in over half the trials with the two drugs.

*Allergic rhinitis* of extrinsic seasonal variety (pollen hay fever) responded almost as well as the drug eruptions. Some of the patients in this class had received preseasonal therapy against ragweed hay fever. All were given small supplies of one of the drugs for use at such times as symptoms developed. Eighty-five per cent of the 60 patients in this group reported success with Pyribenzamine, 19 of these were subsequently given Benadryl for comparison, and all but 4 found the drugs equally effective. Nineteen other subjects were tested clinically with Benadryl alone and experienced relief comparable with that described after Pyribenzamine.

Atopic dermatitis was even less responsive, the results being entirely negative in 4 patients and partial in 1, who noted that the pruritus was controlled. One of 2 subjects with pruritus due to obstructive jaundice also considered the subjective discomfort to have been alleviated after the administration of Pyribenzamine. The wheal, flare and pruritus of dermatographia were reduced if two tablets were administered fifteen minutes before the skin was traumatized with a fingernail stroke. Similarly, the drug afforded definite relief to a young woman who had developed generalized urticaria, angioneurotic edema and critical hypotension a few hours after having received antitetanic horse globulin, the intense itching and the tendency for the arterial tension to drop to shock levels were both controlled by hourly doses of 50 mg administered for four hours.

In general, the experience with these drugs makes it appear that they are most valuable in urticaria, hay fever and in systemic reactions to overdoses of allergenic solution.

*Relative Efficacy in the Same Patient*

Figure 1 indicates the results of trials in 33 patients in whom the effects of first one drug and then the other were established. In 23, the therapeutic influence of the two agents could not be distinguished. Among the remainder, half preferred one and half the other medication. In the group in which equal response to either drug was reported 4 patients detected no influence on their complaints, 7 reported partial control of symptoms, and 12 were

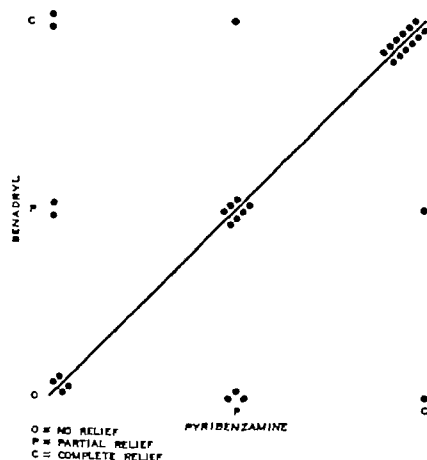


FIGURE 1 *Relative Efficacy of Pyribenzamine and Benadryl in Thirty-Three Patients*

completely relieved. So far as the type of complaint is concerned, 20 subjects in this experiment were ragweed sensitive, 3 exhibited systemic reactions to therapeutic injections, and the remainder were given the histamine antagonists for such conditions as intrinsic asthma, atopic dermatitis and acute and chronic urticarial eruptions.

**Side reactions.** Proportionately, nearly twice as many patients had untoward reactions from Benadryl as from Pyribenzamine (Table 2). Some patients noted more than one side effect. The complaint most frequently observed was drowsiness associated with mental sluggishness. Whereas 61 per cent of patients treated with Benadryl were afflicted in this way, only 20 per cent of those treated with Pyribenzamine gave evidence of sedation. Gastrointestinal disturbances, ranging from nausea, anorexia and epigastric distress to vomiting, diarrhea and abdominal colic, were encountered somewhat oftener after Pyribenzamine than after the other drug. A sense of exhaustion and generalized weak-

ness occurred after 8 per cent of the Benadryl treatments, whereas only 3 per cent of patients treated with Pyribenzamine had this type of side effect. Central stimulation caused insomnia and sensations of nervous tension in 4 per cent of both groups. There were 2 cases of headache, both related to Pyribenzamine. Dizziness was reported by 6 per cent of patients given Benadryl and by 3 per cent of those treated with Pyribenzamine. Muscle twitchings, tenderness and aches and in some cases difficulty in phonation and in co-ordinating movements of the extraorbital muscles were described by 6 per cent of the former group and by 2 per cent of the latter. One patient in each series complained of feeling depressed. An occasional case of numbness of the lips and tongue was detected, the con-

TABLE 2 *Side Effects of Histamine Antagonists in 178 Cases*

Side Effect	WITH PYRIBENZAMINE		WITH BENADRYL	
	NO. OF CASES	PER CENTAGE	NO. OF CASES	PER CENTAGE
Drowsiness	26	20	31	61
Gastrointestinal upset	18	14	5	10
Exhaustion	4	3	4	8
Vomiting and insomnia	3	4	2	4
Dizziness	4	3	3	6
Faulty co-ordination of vocal or extraorbital muscles (twitching and pains)	3	—	3	6
Headache	—	2	—	—
Depression	1	1	1	2
Numb lips and tongue	2	—	—	—
Tinnitus	1	1	—	—
"Hypersensitivity"	—	—	1	2
Exacerbation of cough	1	1	—	—
Totals	6	—	51	—
Percentages of total cases treated	40		71	

dition was ascribed to the local anesthetic action of both drugs. One patient believed that Benadryl provoked a cough lasting for several days, and another was certain that a pre-existing asthmatic cough had been exaggerated shortly after the taking of Pyribenzamine. The former has been listed under the heading of "hypersensitivity" for want of a better classification.

### DISCUSSION

There seems little doubt that the histamine antagonists are of definite value in the symptomatic relief of acute urticaria and of seasonal hay fever. Their value in the prevention or control of manifestations due to overdosage with therapeutic allergens is difficult to appraise. If, as in the experiments of Arbesman,<sup>2</sup> the drug is given shortly before the "overdose," there is always the possibility that on this particular occasion the dose would have been tolerated even without the drug. On the other hand, if one awaits the development of systemic manifestations the drug must be allowed fifteen to twenty minutes for its effect to become apparent. Obviously, such delay would be unwarranted if the situation was at all critical.



One is limited, therefore, to studying the new drugs in cases of relatively mild systemic reaction. Under these circumstances, judgment is clouded by the tendency of mild overdosage reactions to subside spontaneously after twenty or thirty minutes.

Theoretically, it might be expected that such overdosage symptoms as urticaria, hay fever and histamine-like hypotension would be counteracted by the drugs. If bronchospasm developed, however, it would be anticipated that they would prove less effective. Our limited experience with overdosage reactions seems to be in keeping with these theories. It seems probable that the simultaneous administration of adrenalin intramuscularly and of a histamine antagonist orally would ensure prompt relief and sustained control of symptoms other than asthma. In the latter situation it might be wiser to replace the antihistamine drugs with Neo-Synephrin or some similar, orally administered antispasmodic.

Although seasonal hay fever and other extrinsic types of vasomotor rhinitis are symptomatically relieved by the new drugs in a high proportion of trials, the most satisfactory management of hay fever appears to rest on a combination of specific therapy and of symptomatic relief with the antihistaminic agents. Many of the patients came to this conclusion by the end of the 1946 ragweed pollinating season, whether they had omitted their customary "booster" courses and had depended on the drugs alone or had taken injections and employed the drugs only occasionally when necessary. The new drugs play their most valuable role in acute and even in some cases of chronic urticaria because no other satisfactory remedies are available. This remark also applies to such cases of bronchial asthma as respond to Benadryl or Pyribenzamine.

There are important differences in the types and incidences of side reaction that follow the two drugs. Although Benadryl produced sedation in 60 per cent of patients, this fact may be turned to advantage when fatigue, anxiety or insomnia complicates the allergic disorder. The sedative effect is also highly desirable for pruritus. Benadryl should be deliberately selected in such cases. On the other hand, patients whose efficiency and judgment may be impaired by sedation should be given Pyribenzamine for daytime use. Since gastrointestinal complications follow Pyribenzamine some-

what oftener than they do Benadryl, the latter is probably more suitable for patients with abnormalities of gastrointestinal function. It was our impression that the taking of food with Pyribenzamine or of caffeine or benzedrine with Benadryl obviated some of the side effects.

Whereas most patients given first one remedy and then the other reported comparable results with each, a small group responded selectively. It would be well, therefore, to change to the other drug when one gives rise to either undue side reactions or unsatisfactory therapeutic control.

### SUMMARY

Among 150 patients given Pyribenzamine and 53 given Benadryl by mouth, partial or complete control of symptoms was noted by over 80 per cent of those with acute urticaria or allergic rhinitis of seasonal (pollen) origin.

Twenty-three of 33 patients treated first with one and later with the other histamine antagonist obtained equal relief with the two. Of the remainder, 5 preferred Benadryl, and 5 Pyribenzamine.

The side effect most frequently encountered with either drug was sedation, which was noted in 61 per cent of cases after Benadryl and in 20 per cent after Pyribenzamine. The second most frequent side reaction was gastrointestinal disturbance, which developed in 10 per cent of the former and 14 per cent of the latter. Central excitation and other untoward reactions, which were of relatively mild intensity and infrequent occurrence, were observed in about the same proportion of both groups.

Administration of the drugs to allergic persons during "constitutional" reactions in 20 cases produced encouraging results for urticaria, hay fever and mild bronchial spasm, but severer asthma seemed to resist their influence.

The technical assistance of Mrs. Gloria Giarrizzo is acknowledged.

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ACUTE HEMOLYTIC ANEMIA IN PRIMARY ATYPICAL PNEUMONIA PRODUCED BY  
EXPOSURE AND CHILLING\*

R A COLMERS, M D,† AND J G SNAVELY, M D ‡

STAMFORD, CONNECTICUT

ACUTE hemolytic anemia in the course of primary atypical pneumonia has been reported by Dameshek,<sup>1</sup> Finland<sup>2</sup> and others. Elucidation of the mechanism of this form of anemia has not been offered. Clinical evidence shows that such anemia develops coincidentally with high titers of cold agglutinin in the serum. Since most of these reports have been concerned with patients to whom varying amounts of sulfonamides have been given and since acute hemolytic anemia can develop from the administration of the sulfonamides alone, it has been difficult to exclude the drugs entirely as the cause or to establish the acute hemolytic anemia of primary atypical pneumonia as a separate entity. Ginsberg<sup>3</sup> has reported the occurrence of acute hemolytic anemia during the course of primary atypical pneumonia in which no sulfonamide was given.

The patient in the case reported below received no sulfonamide. The clinical and experimental data indicate that exposure and diffuse chilling were instrumental in producing the anemia. These data are in accord with and are an extension of previously known facts. This mechanism has been postulated by Dameshek<sup>1</sup> and Finland<sup>2</sup> in the reports cited above. Their view was based, at least in part, on evidence that the anemia developed before the administration of sulfonamide and that this therapy did not appear to influence the course of the anemia.

## GENERAL CONSIDERATIONS

Increased cold-agglutinin titers in this disease were first described by Clough and Richter<sup>4</sup> in 1918. Their patient had a diffuse bronchopneumonia with the usual course and with objective findings of what would now be called a primary atypical pneumonia. They failed to associate the disease and the serologic changes and assumed the cold agglutinin to be a peculiar hereditary trait. Cold agglutinin was present in the serum to a titer of 1,500 at refrigerator temperature. The properties of this cold agglutinin were studied with classic thoroughness, and with the exception of the agglutination of indifferent streptococci by Thomas et al.,<sup>5</sup> little of significance has been added by subsequent studies. Clough and Richter's patient also showed a transient slight depression of the red-cell count and hemoglobin content.

Of particular interest is the report of the inverse relation between the temperature at which the cold-agglutination tests were performed and the degree of agglutination. The titer, which was highest at "ice chest" temperature, became progressively lower at higher temperatures, and agglutination was abolished at 24°C.

In 1926, Li Chen-Pien<sup>6</sup> reported that cold hemagglutinins found in a patient suffering from cirrhosis and syphilis had similar properties to those in the case reported by Clough and Richter. The inverse temperature effect was demonstrated, and the agglutination was negative at temperatures greater than 20°C. The Donath-Landsteiner test was negative.

In 1939, Wheeler, Gallagher and Stuart<sup>7</sup> described a potent cold agglutination in a respiratory infection similar to that reported by Clough and Richter. These authors also failed to associate the disease and the serologic changes. A study of the properties of the cold agglutinin agreed with the findings of Clough and Richter. In particular, a similar inverse relation between the temperature and the degree of agglutination was observed. The titer was 1:10,240 at 4°C, 1:2,560 at 12, and 1:160 at 22, and no autohemagglutination was present at 30. This patient did not show anemia.

In 1943, Peterson, Ham and Finland<sup>8</sup> noted the association of powerful cold agglutinins with primary atypical pneumonia. Similar cases were then reported from other clinics.<sup>9-10</sup> In 1945 Finland and his associates<sup>11</sup> published a report of cold-agglutinin titers in primary atypical pneumonia, in common diseases of temperate climate and in health. A study of the properties of the cold agglutination<sup>12</sup> reconfirmed the findings of Clough and Richter.

Observation of the hemolytic properties of the cold agglutinin began with the work of Salen,<sup>13</sup> who recognized that this hemolysis did not require complement and was therefore quite different from the Donath-Landsteiner hemolysis. Salen demonstrated hemoglobinuria in a subject with powerful cold agglutinins by immersing the legs in ice water. The entire study is difficult to interpret, since Salen did not recognize the role of mechanical trauma in producing hemolysis. His protocol of method calls for thorough mixing of cells and serum by shaking, transferring and centrifuging.

A series of reports by Stata and associates<sup>14-16</sup> presented clear demonstration of the mechanism of hemolysis of erythrocytes in the presence of

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powerful cold agglutinins Hemolysis was shown to be due to mechanical trauma, such as shaking or tapping, applied to the cold-agglutinated erythrocytes The degree of hemolysis was directly proportional to the heaviness of the cell suspension and the

Thus, the coincidence of the temperatures of cold-agglutinin activity and of the skin may be easily attainable in certain cases  
In view of the above considerations, the following clinical record approaches an experimental protocol

TABLE 1 Pertinent Laboratory Data

DATE	CORRECTED SEDIMENTA- TION RATE (WINTROBE)	MAZZINI BLOOD TEST	NONPROTEIN NITROGEN	SERUM BILIRUBIN*			DONATH- LANDSTEINER TEST FOR COLD HEMOLYSIS	AGGLUTINA- TION FOR STREPTO- COCCUS MG†	REMARKS
				TOTAL	FREE	BOUND			
	mm /hr		mg /100 cc	mg /100 cc	mg /100 cc	mg /100 cc		titer	
3/29	—	—	—	—	—	—	—	—	Sputum culture insufficient for examination, blood culture sterile after 18 da.
3/30	43	—	—	—	—	—	—	—	—
4/5	—	Negative	—	—	—	—	—	—	—
4/9	—	—	29.6	0.61	0.54	0.07	Negative	—	At height of hemolytic crisis examination revealed patient's blood to be Type B and Rh+ rapid spontaneous agglutination of own cells in own serum at room temperature.
4/10	—	—	28.0	1.10	0.84	0.21	—	—	Patient still in hemolytic crisis
4/12	—	—	—	—	—	—	—	120	—
4/22	15	—	—	—	—	—	—	—	—

\*Determined by means of DuBoscq colorimeter with use of cobalt sulfate standards  
†Determined by Dr. Frank Horsfall, Jr.

degree of agglutination Intravascular cold agglutination was demonstrated in vivo when the tissue was adequately chilled Hemolysis was shown to occur in vivo after such intravascular cold agglutination

For details of the ingenious methods employed by these workers, the reports should be consulted Unfortunately, none of the cases presented evidence of anemia The inverse temperature relation previously noted was present in the most thoroughly studied case, but in spite of high titers at low temperatures, the temperature of extinction of agglutination was 16°C Only small parts of the body of the subject were exposed to temperatures below 16°C either clinically or experimentally This patient had gangrenous changes in the tips of the extremities as the result of activity of cold agglutinins during severe exposure<sup>15</sup>

The premise that this mechanism of local hemolysis is the underlying cause of the acute hemolytic anemia associated with powerful cold agglutinins could be tested by reduction of the temperature of a large area of the skin surface and subcutaneous tissue of a suitable human subject to a level at which potent cold agglutinins would be active This degree of cold might be any temperature from 4 to even 37°C, depending on the temperature at which the cold agglutinin was sufficiently high in titer to produce agglutination and lead to subsequent hemolysis Temperature ranges of the exposed skin and subcutaneous tissue depend largely on the room temperature and degree of exposure and are usually from 24 to 34°C After exposure to cold, the skin temperature may fall grossly below this level<sup>17</sup>

in which the previous hypothetical conditions for development of acute hemolytic anemia were satisfied

CASE REPORT

A 21-year-old unmarried woman was admitted to the hospital on March 29, 1946, with the chief complaints of malaise, weakness, chills, fever and cough Three days prior to admission the patient had noticed chilliness, fever and generalized aching Two days later a hacking cough pro-

TABLE 2 Red-Cell Counts and Hemoglobin Data

DATE	RED-CELL COUNT	HEMOGLOBIN	REMARKS
	$\times 10^4$	gm /100 cc	
3/30	4.10	12.5	Patient given cold sponge bath (ice cold alcohol)
4/1	—	—	—
4/3	3.96	12.0	Patient given cold sponge bath
4/7	—	—	Patient given cold sponge bath
4/8	2.07	7.5	Patient given three cold sponge baths in early morning
4/9	—	—	Patient given 1000-cc. transfusion of compatible fresh whole blood
	1.64	4.5	—
4/10	2.45	6.0	Patient given 1000-cc. transfusion of banked whole blood
4/11	3.34	10.5	Patient given 500-cc. transfusion of banked whole blood
4/12	3.21	9.0	—
4/15	3.31	9.5	—
4/18	3.25	10.0	—
4/20	—	—	Patient given 500-cc. transfusion of banked whole blood
4/22	3.85	11.5	—

ductive of a small amount of white mucoid material developed There was no history of blood-tinged or rusty sputum or of pleuritic pain  
The past history revealed that voluntary dietary restrictions had led to the loss of 20 pounds in the 3 or 4 months prior to admission There was no further clinical history of any significance  
Physical examination was negative except for finely crepitant rales in the lower lobe of the left lung posteriorly  
The temperature was 102.2°F, the pulse 100, and the respirations 22 The blood pressure was 128/78

The clinical diagnosis was primarily atypical pneumonia of the lower lobe of the left lung.

Examination of the blood disclosed a red-cell count of 4,100,000 with a hemoglobin of 12.5 gm per 100 cc. and a white-cell count of 9900, with 81 per cent adult neutrophils, 16 per cent small lymphocytes, 2 per cent monocytes and 1 per cent basophils. (The total and differential white-cell counts did not change essentially from admission levels during the first 2 weeks in the hospital.) Urinalysis showed nothing remarkable except on one occasion reported below Table 1 presents the pertinent laboratory data.

Penicillin therapy was begun on the 1st hospital day in doses of 30,000 units every 3 hours but was discontinued after 3 days because it appeared to be of no value. The fever tended to decrease somewhat until April 4, but on the following day there was an upward swing of the temperature with a spiking pattern. Progressive pallor and weakness were observed. The nurse's records reported "dark urine," but these specimens were not saved for examination.

On April 8 the clinical and roentgenologic signs of pneumonia had spread to both lungs. The spleen was enlarged and the hemoglobin had dropped to 7.5 gm per 100 cc., with a red-cell count of 2,070,000 (Table 2) the patient passed swiftly and yet imperceptibly into a serious condition. On the same day the red cells, when mixed with the patient's

at 7 and 26 C increased to 1.5120. In spite of this, no further hemolysis occurred and the patient slowly recovered. Rigid precautions were taken during this period to keep her warm. She was sent home on May 2 with instructions to avoid cold exposure and tub baths.

The temperature chart is presented in Figure 1. The hemolysis *in vitro* is shown in Table 4. The hemolysis is interpreted as due solely to unavoidable trauma to the cells.

#### Experimental Data

On April 30, after recovery had been assured it seemed safe to perform an experiment. The cold agglutinin titer on that day were 1:2560 at 4°C. and 1:40 at 26, and no agglutination was found at 37.

The right arm was immersed for 15 minutes in ice-cold water containing pieces of ice. The patient voided immediately before the immersion, and this urine was saved for control purposes. A sample of blood was obtained from the left arm immediately before immersion. Every precaution was taken to avert adventitious hemolysis. Blood samples were withdrawn from the right arm 15 minutes after the cessation of immersion (30 minutes after the beginning of immersion). Blood samples were drawn from the same arm at 15-minute intervals thereafter. These blood specimens were labeled 0 (control), 30 minutes 45 minutes and 60

TABLE 3 Cold Agglutinins by Tube Method\* at Different Temperatures

DATE	TITER AT 37 C	TITER AT 26 C	TITER AT 7 C	TYPE OF CELLS	PATIENT'S SERUM
In hospital					
4/9	1.5	1:1280	1:1280	Patient's (washed)	Fresh
	1.5	1:1280	1:1780	Type O	Fresh
4/18	1.5	1:5120	1:5120	Patient's (washed)	Inactivated
	1.5	1:5120	1:5120	Type O	Inactivated
	1.5	1:5120	1:5120	Patient's (washed)	Inactivated (complement added)
	1.5	1:5120	1:5120	Type O	Inactivated (complement added)
4/30	0	1:40	1:2560	Patient's (washed)	Inactivated
After discharge					
6/8	0	Not done	1:80	Patient's (washed)	Inactivated
8/14	0	Not done	1:320	Patient's (washed)	Inactivated
9/27	0	0	1:160	Patient's (washed)	Inactivated

\*Procedure consisted of serial dilutions of serum in physiologic saline solution beginning at 1:5. The total volume of serum in addition to physiologic saline solution was 0.5 cc. To each of the tubes 0.2 cc. of cell suspension was added. As indicated, Type O or adequately washed patient's cells were used. All tubes were incubated overnight, and then the agglutination was dispersed by incubation at 37°C. The serum titers are expressed independently of the further dilution produced by the volume of fluid in which the cells were suspended.

own serum, agglutinated in 10 to 20 seconds at 26°C. The clumping was easily visible on gross inspection and resembled that seen in slide typing with potent agglutinating serum. After eight washings with warm saline solution the red cells no longer agglutinated spontaneously, and blood typing could be done.

Cold-agglutination tests showed a titer of 1:1280. The titer at 26 was identical to that at 7°C. the titer at 37°C. however was only 1.5, and the clumping in the 1.5 dilution was dubious. All agglutination could be dispersed by warming of the tubes to 38°C. (Table 3) During the night the temperature rose to 106°F.

In spite of explicit orders to keep the patient warm a nurse gave her three general body sponges using ice alcohol. On the following morning the red-cell count had dropped to 1,640,000, with a hemoglobin of 4.5 gm per 100 cc. The patient looked moribund. A dark brown urine specimen was reported to have been passed in the morning after the sponges, but had been discarded. The next specimen showed no demonstrable hemoglobin by chemical test.

Between April 9 and 11 a total of 3000 cc. of fresh and banked blood was given. The blood was warmed to 37°C in a water bath before delivery to the bedside and was kept warm during administration. No reaction occurred. The absence of any reaction may have been of some importance, since intracellular hemosiderin granules were demonstrated in epithelial cells obtained from the centrifuged urinary sediment on April 13. Between April 11 and 17 at the suggestion of a consultant, 100,000 units of penicillin was given intramuscularly every 2 hours.

During this period the clinical evidence of pneumonitis became more obvious, and the titer of the cold hemagglutinins

minutes respectively. A final specimen was drawn from the same arm 120 minutes after the beginning of exposure. Plans to draw corresponding samples from the left arm had to be abandoned because of residual damage to the veins of this arm as the result of prolonged and intensive intravenous therapy.

After collection of these samples the blood was allowed to clot at room temperature with no agitation. The serum was separated with great care. The warm tubes were then centrifuged to remove any possible residual cells or particulate material. Except for slight difficulty in obtaining the 30-minute specimen (necessitating puncture of the vein), the blood samples appeared to have been ideally obtained. The difficulty with the 30-minute specimen did not appear adequate to account for significant hemolysis *in vitro*.

The patient voided 1½ and 12½ hours after the beginning of immersion of the arm. All the voidings were saved in a dry clean container. After thorough mixing portions of each of these specimens and of the control urine were saved for spectral analyses.

The serum and urine specimens were subjected to spectral analyses\* 36 hours after immersion. The 120-minute sample was not tested.

The control and the 120-minute serums were completely free from any trace of hemoglobin on gross visual inspection. The 30-minute specimen was markedly hemolyzed and the 45-minute specimen showed somewhat less marked hemolysis. The 60-minute specimen showed only the faintest trace of hemolysis, and there was a difference of opinion concerning whether this was actually visible.

\*Performed on a General Electric recording spectrophotometer in the American Cyanamid Laboratories, Stamford, Connecticut.

The spectral analyses of the serums are presented in Figure 2. The control specimen revealed a faint trace of absorption that seemed insignificant and possibly represented an unavoidable minimum of hemolysis. The 30-minute curve disclosed characteristic spectral absorption bands of oxyhemo-

sence of hemoglobinuria suggests that the systemic hemoglobinemia did not reach a sufficient concentration to appear in the urine and was disposed of by some other mechanism. Within a few minutes after immersion, a peculiar dark purple mottling of the immersed portion of the arm was

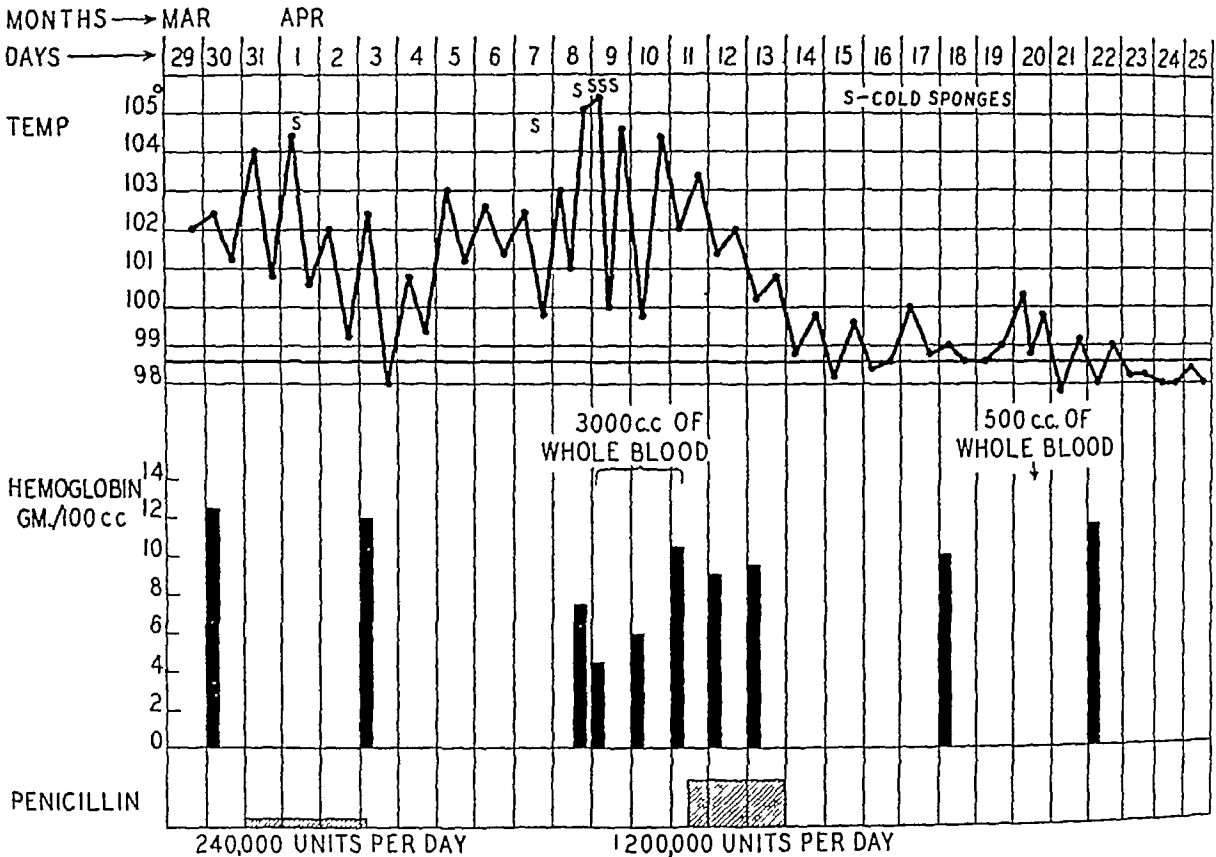


FIGURE 1 Temperature Chart, Hemoglobin Levels and Penicillin Therapy

globin. The 45-minute specimen showed similar absorption bands differing only quantitatively from the preceding specimen. The 60-minute specimen demonstrated the absorption bands of the serum to be markedly reduced and only slightly greater than those of the control serum. This amount of resid-

noticed. Fifteen minutes after removal of the arm from the ice water, this began to disappear, and the skin resumed its normal appearance after 1 hour. The local mottling was thought to be due to reversible intravascular agglutination in the chilled skin and subcutaneous tissue, resulting in ob-

TABLE 4. Hemolysis\* at Different Temperatures

DATE	TITER AT 37°C.	TITER AT 26°C.	TITER AT 7°C.	TYPE OF CELLS	PATIENT'S SERUM
In hospital					
4/9	1 5	1 5	1 5	Type O	Fresh
	1 5	1 5	1 5	Patient's (washed)	Fresh
4/18†	1 10	1 10	1 10	Type O	Fresh
	1 10	1 10	1 10	Patient's (washed)	Fresh
	1 10	1 10	1 10	Type O	Inactivated
	1 10	1 10	1 10	Patient's (washed)	Inactivated
4/30	0	0	0	Patient's (washed)	Inactivated
After discharge					
6/8	0	0	0	Patient's (washed)	Inactivated
8/14	1 10	1 10	1 10	Patient's (washed)	Inactivated

\*No hemolysis was more than a slight trace. Except for the duplicate tests with guinea-pig complement this table does not represent separate tests but merely shows hemolysis read in the cold-agglutinin tubes, independent of shaking.

†Duplicate sets of each test with 4 units of guinea-pig complement showed identical titers.

ual hemoglobin seems significant only as showing a nearly complete cessation of the local hemolysis.

The spectral analyses of urine samples are presented in Figure 3. These are marked 0, 1½ hours and 12½ hours, respectively. None of these samples showed any trace of absorption bands in the zones of oxyhemoglobin. The ab-

struction of the lumens of small vessels, which in turn gave rise to local, mottled cyanosis.

DISCUSSION

Cold agglutination of homologous and heterologous erythrocytes has been sporadically reported in

various diseases and much more regularly in association with primary atypical pneumonia. Occasionally, a hemolytic anemia develops in the course of primary atypical pneumonia associated with powerful cold agglutinins in the serum. Confusion of this type of hemolytic anemia with that associated with sulfonamide therapy has been dispelled by the recent report of a case in which no sulfonamide was given.<sup>3</sup> There seems to be little reason not to regard the acute hemolytic anemia of primary atypical pneumonia as a distinct entity due directly to the action of cold agglutinins on the red cells of the patient. Intravascular hemolysis by cold agglutinins depends on the trauma suffered by previously agglutinated erythrocytes in their passage through fine blood vessels. The degree of destruction of erythrocytes is proportional to the titer of the agglutinins and the heaviness of the cell suspension.

The production of hemolytic anemia seems to depend on many factors, such as the temperature

convenience in discussing the effect of temperature, an arbitrary term, "temperature hemolysis factor," is introduced. This is defined as the maximum tem-

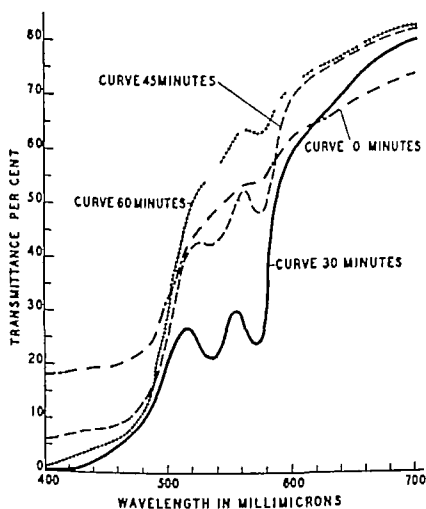


FIGURE 2. Serum Absorption Bands following Chilling

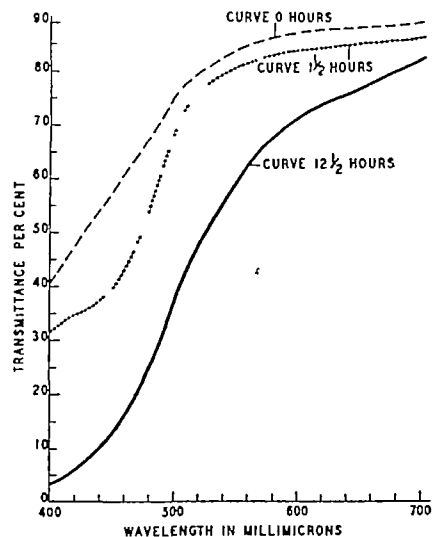


FIGURE 3. Urine Absorption Bands following Chilling

perature at which cold agglutinins are sufficiently active to give intravascular hemolysis. This term is important, since cold agglutination, for the most part, is a phenomenon observed at refrigerator temperatures.\*

The term "cold" is relative, and cold agglutination has been observed repeatedly at temperatures ranging from 20 to 37°C. These ranges coincide with skin temperatures under conditions of ordinary exposure. When the temperature hemolysis factor and skin temperature coincide, hemolysis must occur.

The temperature to which the skin must be lowered to give hemolysis is directly related to the temperature hemolysis factor of the cold agglutinins. Unusual chilling, as in the case presented above, may be necessary for hemolysis if the temperature hemolysis factor is low, but not necessarily if the factor is sufficiently high.

Merely hemolysis does not lead to anemia unless a sufficient quantity of erythrocytes are destroyed.

of potent cold-agglutinin activity, the number of red cells destroyed and the duration of exposure. These are considered individually below.

The temperature factor cannot be divorced from the titer of the agglutinins because of their close inverse relation, as shown by other observers.<sup>4, 5, 7</sup> Since the exact cold-agglutinin titer for production of hemolysis *in vivo* is not known, for the sake of

\*In the experience of one of us (J. G. S.) 20 cases of elevated cold agglutinin titer have been studied. The case presented above is the only one in which activity at 26°C. could be demonstrated and in which hemolytic anemia was present. The titers at 7°C. in these cases ranged from 1:160 to 1:5120 (expressed in terms of dilution of serum).

This quantity must be related to the volume of tissue exposed and the duration of exposure. We have no evidence on which to base any estimation of the proportionate, quantitative effect of these factors.

The production of acute hemolytic anemia thus depends on the coincidence of a number of variables of uncertain proportionate importance. Under such circumstances a dramatic episode may be needed to call attention to the precipitating factor or factors. In the case reported above, a marked anemia developed without much hint of its cause until the overnight drop of 40 per cent in the hemoglobin following severe chilling literally forced this factor to our attention.

A few points of the clinical record need clarification. One of these is the absence of proof of hemoglobinuria. The nurse's observations clearly pointed to this, but objective proof was lacking, owing to the inadvertent discarding of the urine samples. Neither was there clinical evidence of jaundice, although there was a slight elevation of the total serum bilirubin. The objective proof of the destruction of red cells rested largely on the red-cell counts, hemoglobin determinations and clinical observations. Since the counts in relation to corresponding blood hemoglobin contents fell within the expected range of error, fallaciously low counts due to intrapipette hemolysis or other technical errors seem to have been eliminated.

Furthermore, all the counts except the first two were mean values obtained from multiple determinations in which warm diluent, warm pipettes, shaken at incubator temperature, and warm hemocytometers were used to avoid such difficulties. The total change in the counts was too large and too rapid to be accounted for in any other way than by intravascular hemolysis or massive hemorrhage. There was nothing to suggest a hemorrhage of such magnitude.

To explain the absence of jaundice, the mode of disposal of the released hemoglobin is of prime importance. Destruction of the same number of red cells in other conditions usually results in marked bilirubinemia and clinical jaundice. We are forced to assume that a large portion of the hemoglobin was disposed of in the urine in this case. There appears to have been a difference between the mode of disposal of intravascularly released hemoglobin and the extravascular destruction of red cells. This hypothesis is under investigation. Intracellular hemosiderin granules in the cells of the urine sediment, in the absence of transfusion reaction, suggested renal disposal of the hemoglobin.

#### SUMMARY

A case of primary atypical pneumonia in which potent cold agglutinins resulted in an acute hemolytic anemia in the absence of sulfonamide medica-

tion is presented. At the time of the development of maximum anemia, cold agglutination was present in the serum with identical titers at 25 and 7°C. At that time a trace of agglutination was even present at 37°C. The anemia developed coincidentally with the administration of cold alcohol sponges and exposure.

With recognition of the cause of hemolysis, further, and possibly fatal, hemolysis was prevented by rigid precautions against chilling, in spite of even higher titers of agglutinins found later in the disease.

A mechanism of local hemolysis was demonstrated experimentally, confirming the findings of Stats and his associates.

The temperature factor of the cold agglutinin activity is just as important as the level of cold agglutination at 7°C. The cold-agglutination test should be done routinely in triplicate racks incubated at 7, 26 and 37°C. Although an arbitrary level cannot be given, any appreciable titer of cold agglutinins at or above 26°C should probably be considered potentially dangerous.

Acute hemolytic anemia due to the mechanism demonstrated should be avoidable.

Since cold sponges, administration of antipyretic drugs and ordinary exposure are routine procedures in the treatment of febrile patients, the significance of these factors in the production of acute hemolytic anemia in primary atypical pneumonia may easily be overlooked. Alertness to these factors in future cases may make it possible to evaluate the general application of the case reported.

This appears to be the only case of hemolytic anemia in primary atypical pneumonia in which a mechanism of hemolysis has been elucidated. The hypothesis is strongly supported by clinical and experimental data.

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## PREFRONTAL LOBOTOMY IN THE CHRONIC DEPRESSIVE STATES OF OLD AGE

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THE operation known as prefrontal lobotomy was first performed by Moniz<sup>1</sup> in 1936. Since that time, the procedure has been widely employed in many types of mental illness in which the course of the disease has been prolonged and the outlook desperate. The operation consists of the cutting of a part of the fibers between the thalamus and prefrontal lobes.<sup>2,3</sup> The rationale has been to disassociate, by surgical means, pathologic thinking from its emotional reverberation. This, of course, is a vast oversimplification of an extremely complex psychologic and neurophysiologic event. The results, when successful, have relieved patients of overwhelming anxiety, obsessive thinking, depression and other crippling emotional reactions. The best results have been obtained in chronic depressions and in some obsessive-compulsive states in which there is marked anxiety. It has been the experience of most observers that the results in chronic schizophrenia are far from satisfactory.

Mental illness in old age is usually regarded as a hopeless problem. The physician has an attitude of therapeutic nihilism and, as a rule, tends to classify all syndromes as organic and to emphasize the deteriorating aspects of senility. The realities of old age, as well as the lack of physical and mental resiliency, make most types of therapy extremely difficult, even when it is recognized that the essential features of the psychosis are those of a depression. It is a frequent clinical experience that such patients react poorly to electric shock therapy. For this reason, the following case histories of 4 women, over sixty years of age, with chronic depressions whose symptoms were greatly alleviated by means of prefrontal lobotomy are reported.

CASE 1. The patient was a 73-year-old woman whose family history was replete with mental illness. A daughter had recurrent manic-depressive episodes, a son had a severe anxiety state, and there was a strong familial history of mental illness in the patient's siblings and collateral relatives. The family described her as a sensitive person who

tended to worry over details. On the whole however she got along with her friends and showed no mental abnormalities until the age of 63. The depressive episodes, at first, lasted only a few months and usually occurred in the spring.

In 1944 the patient began to feel depressed in the winter, when she was first seen by us. She was quite depressed and extremely agitated and hypochondriasis was marked. In April 1945 she was sent to an institution where she remained for several months without any improvement. Finally, her condition became so marked that she was given electric shock treatment in October, despite her advanced age and in the presence of auricular fibrillations. She again received electric-shock therapy in November and December without improvement.

Because of the pronounced agitation and intractable depression a prefrontal lobotomy was performed on December 22 by Dr James L. Poppen. Almost immediately the patient's mood improved. There was some difficulty in control of the bladder for about 4 weeks. During the 3rd postoperative week she was playing bridge. Subsequently, she was relaxed, and there was no recurrence of the depression or agitation. She carried on her household duties as before and she was quite capable of meeting people adequately. There was no obvious change from the level of intellectual abilities that she had maintained prior to operation. So far as the family was concerned, there was no change in personality or temperament, and she was much more agreeable to live with than at any time in many years. When last seen she was pleasant, courteous and alert and gave every evidence of being a reasonably content elderly woman who was aging in a satisfactory fashion.

CASE 2. This patient, a 62-year-old woman had a sister who had been in a mental institution for many years because of a chronic depressed state. Throughout her life, the patient had had occasional episodes of depression usually lasting several months at a time and associated with strong feelings of hopelessness and marked somatic disturbance. She was first seen in May 1944 when she had been severely depressed for 10 months. She was given four electric-shock treatments with partial recovery and in October of the same year she was given five more. Subsequently she did quite well for a year when there was a recurrence of depression for which she received seven electric shocks. She showed only temporary improvement, and shortly thereafter the depression and agitation recurred. She was unable to sleep and lost considerable weight because she refused to eat.

In January 1946, a prefrontal lobotomy was performed by Dr Poppen. Almost immediately the patient became cheerful, and within several months she had gone back to managing her household. This improvement has continued until the present time. The husband stated that she had been uniformly happy and untroubled. When unusually tired she seemed quieter than formerly, but never depressed and readily recovered from the fatigue. She was entirely capable of controlling the family budget, planning her work, shopping and so forth. She enjoyed meeting people—even pouring at a faculty tea. Her intellectual capacity was no different from that in the past. Friends told the husband that in the 20 years they had known the patient, she had never seemed so well and so normal. He could detect no personality

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changes except the absence of fear. Occasionally, she seemed somewhat detached and showed a slight loss of initiative, but these episodes were so slight as to be scarcely worthy of mention. The really significant thing was that she was able to meet greatly increased responsibilities better than for a long time.

**CASE 3** A 67-year-old woman was first seen in January, 1942. Her family history was strongly positive for manic-depressive psychosis. A brother had committed suicide, and a sister had had several admissions to a state hospital. The patient had had at least six episodes of mental disease during the previous 10 years. The periods consisted of overactivity lasting several months, associated with euphoria, and were followed by periods of exhaustion, depression and loss of energy. As the years went on, the attacks became more prolonged, and the depression more pronounced. Freedom from symptoms was of brief duration. As in the other cases, there was no delusional formation, no sense of guilt and no retardation. Chiefly, there was a feeling of depression and an absence of energy, drive and interest.

During the next 4 years, the patient was seen during four episodes, in each of which the depressions were terminated by electric-shock treatment until the last attack, which remained intractable to shock therapy, the patient had no remission, remaining completely depressed for 7 months prior to prefrontal lobotomy.

The operation was performed in April, 1946, by Dr. Poppen. The patient's mood changed almost immediately, and she was subsequently pleasant and relaxed. There was no return of depression, but from time to time she complained of a sense of fatigue and weariness. It appears almost that the deep affective disturbance of depression had been altered by the operation in some manner, so that it was experienced as a considerably more endurable reaction. The patient met people well, and intellectually she seemed normal. On the whole, the operation was extremely successful.

**CASE 4** A 53-year-old woman was first seen in 1937, when she had been depressed for over a year. There was a history of two previous episodes, the first occurring in the third decade, the other in the fifth. During these attacks, she was depressed, had marked insomnia and anorexia, lacked endurance and was extremely agitated. There were no delusions, feelings of guilt or paranoid trends. She was next seen in 1942. In the interval, she had been in a mental institution, where she was given electric-shock treatment. She improved for a short while, but rapidly slipped back into the previous condition. In 1946 the patient was seen again, and in view of the fact that the depression had lasted in an unmitigated fashion for 10 years despite electric-shock and other treatment, it was decided that prefrontal lobotomy was urgently indicated.

In July of that year, the operation was performed. The patient was quite confused for several weeks after the operation, but then began to show definite signs of improvement. Subsequently, she functioned at a much higher level than previously. She visited friends and did some shopping and entertaining at home for the first time in almost a decade. She herself stated that she had periods in which she felt rather low and lacked energy, but this was not obvious to her family, and in general she behaved in a more socially adequate fashion. There was no impairment of intelligence or judgment.

The cases described above have several features in common. First of all, the patients were all women in the declining years of life who had been mentally ill for years. Secondly, the clinical syndromes were similar. The outstanding features were depression, lack of energy and enthusiasm and retreat on the basis of an overwhelming disturbance in the affect of the patient. In none of these cases was there marked retardation of speech or strong suicidal drives, and paranoid or guilt reactions were not apparent. Thirdly, they all responded remarkably to prefrontal lobotomy. In each case there was a radical improvement both in the way the patient herself felt and in the manner in which she behaved. This resulted in a marked alleviation of the tension and distress that are pronounced in the depressed states. In no case was there obvious intellectual impairment. Of course, none of these women had led an intellectual life in the past, nor had they held positions of responsibility, but judging by past performances — the ultimate criterion — they behaved in a far more useful and socially adequate fashion after the operation. The operation in each case relieved the patient of depression in a striking manner. In at least 1 case, however, a definite sense of fatigue remained, possibly owing to the same factors that were responsible for the depression, but with the severance of the cortico-thalamic pathways, the process is experienced as fatigue rather than as a deeply lowered mood.

The point that is especially emphasized is that old people with chronic depressions should not be regarded as hopeless and doomed to live out their remaining years in retreat and unhappiness. Properly performed, prefrontal lobotomy can do them no harm. We have, as yet, experienced no failures, and it should be emphasized that only cases in which at least a year had elapsed since the operation are reported. The alternative to the operation is to add the misery of melancholia to the disabilities of old age.

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## MALIGNANT TESTICULAR NEOPLASMS IN INFANCY\*

## Report of a Case with Six-Year Survival

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**M**ALIGNANT tumors of the testicle in children are rare. Dargeon,<sup>1</sup> reviewing malignant tumors in 1557 children collected from five major sources, found 211 cases involving the genitourinary tract. Matassarin<sup>2</sup> quotes Gilbert, who collected 5500 cases of all tumors of the testicle reported in detail from 1803 to 1942 and observed only 131 cases in children under fifteen years of age.

There are several reports of testicular neoplasm in children in the early literature.<sup>3-5</sup> These have been responsible for the frequently quoted opinion that "there have been numerous reports of malignant tumors, usually teratomas in the newborn."<sup>6</sup> Wells,<sup>6</sup> however, in a classic article on congenital malignant neoplasms, pointed to the lack of actual proof that the testicle is the seat of congenital cancer. He mentioned several doubtful cases from the early literature and concluded as follows:

No more recent reports [after 1900] can be found indicating congenital or even early infantile malignant growth in the testicle, which makes all earlier reports even more doubtful. Of 100 malignant testicular tumors reviewed by Tanner (1922) only one occurred before the seventeenth year. In a review of malignant disease of the testicle Dew (1926) mentioned only two cases in infants.

It is worthy of note that only four histologic reports of malignant testicular tumors in infants could be found. Two of these are cited by Wells,<sup>6</sup> as follows:

A typical case is that of Philipp in which the testicle was enlarged at birth. Not until traumatized in the third year did it grow rapidly and on removal, sarcomatous degeneration of a growth diagnosed as teratoma was found. MacLennan also reported a case in which enlargement of the testicle was present at birth with resection at the eleventh month, followed by development of metastases in abdominal and cervical glands and death in two weeks. Histologically it was considered to be adenocarcinoma.

The recent literature provided two additional case reports, one of which describes a seven-month-old infant with enlargement of the left testicle noted one month prior to treatment.<sup>7</sup> The patient was treated by simple orchidectomy and postoperative radiation and was reported living and well after a follow up study of four and a half months. The diagnosis was embryonal adenocarcinoma. Another case was noted three days after birth in the right

testicle.<sup>7</sup> Orchidectomy was performed, and a diagnosis of Wolffian epithelioma was made. The authors report the case as unique in the literature of Argentina. The diagnosis in the last case might well correspond with that of the two preceding cases.

The following case of adenocarcinoma of the testis is considered worthy of report because of the rarity of the neoplasm so early in infancy and because of the long follow-up period with apparent cure.

A S (BIH 54467) an 8 month-old boy was admitted to the hospital on September 4, 1940, because of a swelling of the right testicle. The infant had been born after a full-



FIGURE 1 Photograph of the Scrotum on Admission

term normal delivery. At birth the child showed no signs of injury and weighed 9 pounds. At an early age the scrotum was noted to be somewhat larger than normal but both testicles were felt to be of normal size within the scrotum. An attempt was made at the time of the first visit to the Tumor Clinic on October 8 to obtain specific information on this point. The mother stated that she had noted an

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enlargement in the scrotum immediately after the child's birth. This was pointed out to the family physician during the course of an examination at the age of 1 month, but he did not consider that there was anything abnormal in the scrotum. At 4 months a mass was noted in the scrotum. A physician was consulted at that time and called it a hydrocele, deciding that no treatment was indicated. Since a brother of the patient had had a similar swelling, which had been called a hydrocele and disappeared at the age of 15 months, the mother had accepted this advice with confidence and had not hastened to consult a physician again. The swelling of the right testicle felt alternately hard and soft but was never reducible. It had not grown much in size since it had first been noted but had become consistently harder. The child had gained normally in weight, the weight on admission being 23 pounds. No signs other than the scrotal mass had been noted. On August 30 the mother had

tion of the urinary sediment revealed occasional white cell and 1 or 2 red cells per high-power field, but no casts. The Aschheim-Zondek test was negative.

X-ray examination of the lungs was negative. There was no evidence of metastatic lesions in the shoulders, rib dorsolumbar spine, pelvis and hips. X-ray study of the scrotum revealed a large soft-tissue mass in the right testicular region in which no calcification was noted.

On September 12 a right orchidectomy was performed with ligation and transection of the spermatic cord at the level of the external inguinal ring. No hydrocele was present.

Gross pathological examination disclosed that the tumor weighed 49 gm and measured 5.5 by 4.5 by 4.0 cm (Fig. 2). It appeared completely encapsulated by reddish-tan fibrous tissue. The tumor mass occupied most of the submitted specimen, and was covered by a thin, glistening tan membrane. There was no gross evidence of remaining testicular



FIGURE 2 Photograph of the Tumor on Section, Showing Gelatinous Appearance and Areas of Hemorrhage, Necrosis and Cystic Change

again consulted a physician, who had advised admission to a hospital.

Physical examination revealed a chubby, somewhat pale child. The skin was normal. Abdominal examination revealed no masses. No inguinal lymphadenopathy was noted. The penis had been circumcized. The scrotum was considerably enlarged and tense (Fig. 1), but the overlying skin was not reddened, edematous or warm. Palpation revealed the left testicle to be normal in size and consistence. It was pushed far over to the left by a large mass in the region of the right testicle. The right testicle could not be discerned. In the right side of the scrotum there was an egg-shaped mass measuring about 6 cm in its greatest diameter. The mass seemed tense rather than hard in consistence. Its surface was smooth. There were no masses in the inguinal canal. The mass did not transilluminate light. No impulse was transmitted when the child cried or coughed. The overlying skin was freely movable. The mass could not be reduced or displaced toward the inguinal region. The perineum was normal. Rectal examination was not done.

Examination of the blood disclosed a red-cell count of 4,640,000, with a hemoglobin of 80 per cent, and a white-cell count of 7400, with a normal differential count. Examination

of the urinary sediment revealed occasional white cell and 1 or 2 red cells per high-power field, but no casts. The Aschheim-Zondek test was negative.

X-ray examination of the lungs was negative. There was no evidence of metastatic lesions in the shoulders, rib dorsolumbar spine, pelvis and hips. X-ray study of the scrotum revealed a large soft-tissue mass in the right testicular region in which no calcification was noted. On September 12 a right orchidectomy was performed with ligation and transection of the spermatic cord at the level of the external inguinal ring. No hydrocele was present. Gross pathological examination disclosed that the tumor weighed 49 gm and measured 5.5 by 4.5 by 4.0 cm (Fig. 2). It appeared completely encapsulated by reddish-tan fibrous tissue. The tumor mass occupied most of the submitted specimen, and was covered by a thin, glistening tan membrane. There was no gross evidence of remaining testicular

In the areas where it was scanty the stroma appeared loose, wavy and myxomatous and the neoplastic cells were well preserved. In other areas the stroma was necrotic and contained degenerating neoplastic cells. In a few places complete necrosis to acidophilic amorphous debris was present. A few focal hemorrhagic areas were also encountered. Necrosis and hemorrhage were less frequent in the compact cellular areas of neoplastic tissue where the cells were fairly well preserved and where attempted acinus formation was present. The tumor was surrounded by a thick fibrous capsule which contained remnants of both flattened and well preserved seminiferous tubules. The capsule was slightly invaded by neoplastic cells, and these areas of invasion exhibited infiltration by chronic inflammatory cells at the growing edge of the tumor. The large vacuolated cells seen in the tumor suggested embryoma but the attempted acinus formation suggested carcinoma of the testis. The diagnosis was adenocarcinoma of the right testis.

The postoperative course was uneventful. Healing occurred by primary union and the patient was discharged on the 12th postoperative day in excellent condition.

The patient was followed in both the Tumor Clinic and the Genitourinary Clinic. Radiation therapy was not given. The child developed normally, both physically and mentally. Five months postoperatively examination revealed several firm discrete, freely movable lymph nodes in the right groin and a few smaller ones in the left. This was considered to be secondary to mild penile irritation. In January 1942 and again in January, 1947, x ray study of the chest disclosed no evidence of metastatic disease. Intravenous pyelography on the latter occasion was likewise negative. The child was alive and well when last seen in January, 1947. It was noted that the inguinal lymph nodes had not changed in size during a 6-year period of observation. He appeared to be somewhat smaller than other children of his age.

although x ray studies of the long and flat bones revealed no retardation in bony growth.

### SUMMARY

A case of malignant testicular tumor in an infant is reported. This appears to be one of the few authenticated case reports of malignant testicular neoplasm occurring in the early months of infancy. Another interesting feature of this case is the six-year survival period, with apparent cure. For a tumor characterized by such a high grade of malignancy and rapid growth in the first years of life, this long survival period is noteworthy. It represents the only reported five-year survival of an infant with a malignant testicular neoplasm.

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## MEDICAL PROGRESS

### SERUM LIPIDS AND THEIR VALUE IN DIAGNOSIS\*

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THE serum and the lymph fluid not only are the transport medium for all substances absorbed in the intestines but also contain substances that have originated as a result of intermediary and cellular metabolism. It may therefore be assumed that lipids found in the cells of the organs should also be present in the serum. Such an assumption corresponds only partly with the actual analytical findings. The concentration of certain lipids, although fairly high in the cells of organs, is so low in the serum, and the amount at the disposal of chemists working in the clinical laboratory so small, that present methods are not sensitive enough for their determination.

The lipids important for human physiology and pathology are classified as follows:

**Saturated fat:** glycerol esters of various saturated and unsaturated fatty acids.

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**Monoaminophosphatides:** fatty acid esters of a phosphorylated polyvalent alcohol, combined with a nitrogen-containing group. Their phosphorus-nitrogen ratio is 1:1. (Some monoaminophosphatides contain other organic groups in addition to those already mentioned.)

**Lecithins:** phosphoric acid diesters of diglycerides and choline.

**Lysolecithins:** phosphoric acid diesters of saturated monoglycerides and choline.

**Cephalins:** contain their total nitrogen in form of a primary amino group (ethanolamine or serine).

**Phosphatidyl ethanolamines:** phosphoric acid diesters of diglyceride and ethanolamine.

**Phosphatidyl serines:** hydrolysis products — fatty acids, phosphoric acid, polyvalent alcohols, serine.

**Plasmalogens (acetalphosphatides):** phosphoric acid diesters of a higher fatty aldehyde acetal of glycerol and of ethanolamine.

**Inositol phosphatides:** obtained from brain, soybeans and bacteria.

**Phosphatidic acids (cardiolipins):** hydrolysis products — fatty acids, polyvalent alcohols, phosphoric acids (bound as a monoester).

**Phosphatides of acid fast bacteria:** hydrolysis products — phosphonic acids, polyhydroxyl compounds (such as inositol), fatty acids with straight and branched chains.

**Diaminophosphatides (sphingomyelins):** acid amide of sphingosine with fatty acids (ceramides) in ester linkage with phosphorylcholine.

**Cerebrosides:** acid amides of fatty acids with sphingosine or dihydroxyphingosine in glucosidic linkage with galactose or glucose.

*Sulfuric acid esters* derived from *cerebrosides*  
*Gangliosides* structure unknown, hydrolysis products — sphingosine, neuraminic acid, fatty acids and galactose or glucose.

*Sterols*

- Cholesterol and its esters derived from animal tissues
- Cholesterol and its esters derived from plants
- Hydrocholesterols
- Vitamin D
- Steroid sex hormones
- Bile acids

To facilitate an understanding of the roles of the lipids in human disease it appears necessary to discuss the clinical physiology of lipid metabolism

\* \* \*

NEUTRAL FAT

Hyperlipemia — that is, the increase of neutral fat in the serum — is visible to the naked eye because

however, there is no hyperlipemia It should be emphasized that for the routine analysis of blood for neutral fat, the patient should always be examined in a fasting state

*Retention Hyperlipemia*

Hyperlipemia may be caused by a sluggish removal of neutral fat from the blood stream into the fat depots and into the organs that metabolize fat. The mechanism of such a disorder is not clear at present It may be a neuroregulatory dysfunction or an anatomic change in the wall of the capillaries from which the neutral fat passes into the tissue spaces This form of retention hyperlipemia is relatively rare, and its clinical designation is "idiopathic hyperlipemia " It may occur as an inherited disorder,<sup>2-5</sup> or it may occasionally be observed in

TABLE 1 *Lipid Partition of Serums and Liver in a Case of Idiopathic Hyperlipemia*<sup>9</sup>

LIPID	RANGE FOR NORMAL LIVER	LIVER IN IDIOPATHIC HYPERLIPEMIA	RANGE FOR NORMAL SERUM	SERUM IN IDIOPATHIC HYPERLIPEMIA
	gm /100 gm	gm /100 gm	mg /100 gm	mg /100 gm
Total cholesterol	2.1 - 2.6	2.52	150-260	379
Free cholesterol	0.44-0.55	0.73	40- 70	158
Cholesterol esters	1.50- 2.15	1.79	70- 75*	60*
Total phospholipid	9.0 -11.0	10.05	150-250	465
Sphingomyelin	0.3 - 0.5	1.44	10- 30	13
Cephalin	3.0 - 5.5	3.05	0- 30	Traces
Lecithin	3.0 - 6.0	5.56	100-200	452
Total fatty acid	8.6 -13.0	9.45	200-450	3115
Neutral fat†	1.4 - 4.0	1.22	0-150	2740

\*Percentage of total cholesterol

†In idiopathic hyperlipemia the neutral fat is extremely high in the serum but in the range of normal in the liver

the serum loses its transparency and becomes milky or even creamy in appearance It should be emphasized that an increase of cholesterol or phospholipids without an increase of neutral fat never causes a milky serum The designation "hyperlipemia" should be exclusively reserved for an abnormal increase of neutral fat in the serum, whereas the terms "hyperlecithemia" and "hypercholesterolemia" should be used to designate the increase of these respective lipids in the serum Hyperlipemia is usually accompanied by hypercholesterolemia and hyperlecithemia, whereas hypercholesterolemia and hyperlecithemia occur without hyperlipemia in essential xanthomatosis of the hypercholesteremic type, as well as in xanthomatous biliary cirrhosis, as pointed out below

*Postprandial Hyperlipemia*

This is a physiologic occurrence after the intake of a fatty meal The peak is observed within three to five hours Formerly, it was erroneously believed that hyperlipemia is found in obese people On occasions postprandial hyperlipemia may persist for an unusually long period in obese persons If the serum is examined in the postabsorptive state,

single cases with and without secondary eruptions of skin xanthomas The lipid partition in a typical case is given in Table 1 Since slight glycosuria is present in some cases, the diabetes was formerly considered the causative factor of the hyperlipemia In these cases, however, the hyperlipemia, as well as the glycosuria, disappears after the patient has been given a diet low in neutral fat<sup>6</sup> Insulin in these cases has no effect on the hyperlipemia Idiopathic hyperlipemia with hepatosplenomegaly and secondary xanthomatosis of the Bürger-Grütz type also probably belong to this group.<sup>6 7</sup>

*Transportation Hyperlipemia*

Hyperlipemia may occur as the result of an increased rate of transportation from the fat depots to the tissues The classic example of this type of transportation hyperlipemia is observed in untreated, severe diabetes mellitus The hyperlipemia in untreated severe diabetes disappears with insulin treatment but does not respond to a diet low in neutral fat It is essential to distinguish patients with severe diabetes and transportation hyperlipemia<sup>8</sup> from those with idiopathic hyperlipemia and slight diabetes, because of the difference in

treatment. The former are severely sick, and in the latter, who seem to be healthy, the hyperlipemia is accidentally observed because of acute xanthomatous eruptions. The hyperlipemia observed in chronic pancreatitis,<sup>10-12</sup> as well as in glycogen-storage disease (von Gierke's disease),<sup>13-16</sup> is also considered to be the result of an increased rate of transportation from the fat depots to the organs that metabolize fats.

The mechanism of hyperlipemia and hypercholesterolemia observed in nephrotic conditions, such as lipid nephrosis, the nephrotic state of glomerulonephritis and renal-vein thrombosis, is at present not definitely clarified. It may be assumed that an increased rate of fat transportation also plays a part in these conditions.<sup>14-18</sup>

### PHOSPHATIDES

The functions of the phosphatides in the organism, so far as they are known, may be distinguished as those pertaining to the intracellular metabolism and those playing a part in the transport of fatty acids. The monoaminophosphatides important for the transport of fatty acids are the lecithins, whereas the cephalins and sphingomyelins are found and retained mainly within the cells. The concentration of the latter in the serum is therefore low. In determining the total phospholipids of the serum 70 to 90 per cent may therefore be evaluated as lecithin. The significance of the lecithins in the transportation of fatty acids was shown by Sinclair and his co-workers<sup>19-22</sup> and by Artom and his associates.<sup>23, 24</sup> An intermediary of lecithin metabolism, glycerylphosphorylcholine, was isolated by Schmidt, Hershman and Thannhauser.<sup>25</sup> The occurrence of this substance in the intestinal mucosa provides a simple explanation for the rapid incorporation of ingested fatty acids into the phosphatide fraction.<sup>19-22</sup> The formation of glycerylphosphorylcholine from lecithin is effected by the action of a specific intracellular enzyme, lecitholipase.<sup>26</sup>

The liver is the main organ for phospholipid synthesis. Fishler, Entenman and Chaikoff,<sup>27</sup> using radioactive phosphorus, furnished strong evidence that the liver is the main site of plasma phospholipid (lecithin) formation. Hepatectomized dogs, receiving radioactive sodium phosphate intraperitoneally, showed only minute amounts of radioactive plasma phospholipids six hours after its injection, in contrast to control animals. Despite their reduced ability to form plasma phosphatides (lecithin), the hepatectomized animals were capable of synthesizing phosphatides at a normal rate in the kidneys and intestines.

Choline and choline are present in the monoaminophosphatide molecule. The lipotropic effect of choline and its precursors on the fatty livers of choline-deficient rats and of depancreatized animals has been demonstrated by various authors.<sup>27-29</sup> The amounts of phospholipids, especially those con-

taining choline, are considerably reduced in choline-deficient rats.

It is, however, not proved whether choline or its precursors, the phospholipids, have any curative effect on fatty livers of heterogeneous etiology in human beings. The results of experiments on rats are not necessarily in conformity with bedside experience. The concentration of phospholipids in the serum is not diminished in patients with fatty livers from various causes.

The acetalphosphatides were first discovered by Feulgen<sup>30, 31</sup> in the cytoplasm of cells of all tissues and designated as plasmalogens. Although their function is unknown, their structural relation to cephalin gives a hint of their significance in the intracellular metabolism. No attempts have been made to isolate and determine this group of substances in the serum of human beings.

The concentration of cephalins and sphingomyelins in the serum, in contrast to the lecithins, is low and varies only slightly in healthy persons. These lipids are metabolized mainly within the cells, where they are formed. If changes occur in the total phospholipid concentration in the serum, they should be evaluated for their lecithin component.

In Niemann-Pick disease the concentration of sphingomyelin increases enormously in all organs with the exception of the brain. The serum of patients with Niemann-Pick disease, however, does not contain more sphingomyelin than that of normal subjects. The sphingomyelin is apparently retained in the cells where it is formed.<sup>32-34</sup> An analysis of the lipid content of the organs, serum and ascitic fluid in Niemann-Pick disease is presented in Table 2.

### CEREBROSIDES

The cerebroside is an intracellular lipid. These substances are found in substantial quantities in normal brain tissue, where they are present as galactosidocerebrosides ranging from 40 to 60 per cent of dried tissue. The amount of cerebroside in normal visceral organs is minute (0.1 to 0.6 per cent). Klenk<sup>35</sup> reported galactosidocerebrosides, as well as glucosidocerebrosides, in normal visceral organs. Both substances are determined quantitatively by the method of Ottenstein, Schmidt and Thannhauser,<sup>37</sup> in which small but measurable quantities of galactosidocerebrosides are found in normal visceral organs, whereas glucosidocerebrosides are found only in traces.

Carter, working on the lipid fraction of several hundred liters of serum provided by the plasma studies of Cohn and his group during the war, was able to isolate and identify minute amounts (approximately 100 mg.) of cerebroside from 200 liters of plasma.<sup>36</sup> That these substances cannot be detected in 10 to 50 cc. of serum available for clinical determination is therefore not surprising. For practical

purposes the serum may be considered as lacking cerebrosides in determinable quantities<sup>37-39</sup> The cerebrosides are built and metabolized within the cells where they are encountered In contrast to serum, normal red cells show cerebrosides in measurable amounts Dried red cells contain 0.2 per cent, consisting entirely of galactosidocerebrosides<sup>37</sup>

In Gaucher's disease the cerebrosides are accumulated in reticulum cells and histiocytes of the spleen, liver, lymph nodes and bone marrow (4 to 20 per cent) In contrast to the organs, the serum of patients with Gaucher's disease, like that of normal subjects, does not contain measurable quantities of cerebrosides,<sup>37</sup> and the concentration of cerebrosides in the red cells is not elevated above normal For these reasons the analysis of serum and red cells for cerebrosides cannot be used for diagnostic purposes in Gaucher's disease

Aghion<sup>40</sup> and Halliday and his co-workers<sup>41</sup> found that the cerebrosides that are accumulated in the

cell, which may originate from an increased synthesis and retention of cholesterol in the cell itself — this process is effected without increased supply of cholesterol and cholesterol esters from the bloodstream, and extracellular precipitation or crystallization of cholesterol, which may be observed within the inflamed wall of the gall bladder or the degenerating wall of an arteriosclerotic vessel, which may occur without an increase of cholesterol in the serum and which is due to degenerative changes of the surrounding medium altering the physicochemical state of substances that are not in ionized solution in bile or serum, like cholesterol and part of the calcium

The first and the second mechanism may result in xanthoma-cell (foam-cell) formation characteristic of the various types of xanthomatoses

Thannhauser and Magendanz<sup>42</sup> and Thannhauser<sup>44</sup> classified the xanthomatous disorders according to the laboratory findings in the serum

TABLE 2 Lipid Partition of the Organs, Serum and Ascitic Fluid in Niemann-Pick Disease<sup>45</sup>

LIPID	SPLEEN IN NIEMANN-PICK DISEASE	NORMAL SPLEEN	KIDNEY IN NIEMANN-PICK DISEASE	NORMAL KIDNEY	LIVER IN NIEMANN-PICK DISEASE
	% of dried tissue	% of dried tissue	% of dried tissue	% of dried tissue	% of dried tissue
Total cholesterol	6.73	1.8-2.4	2.82	1.4-2.8	7.00
Free cholesterol	6.70	1.0-1.1	2.81	1.0-1.1	4.50
Cholesterol esters	0.03	0.7-1.3	0.01	0.5-1.7	2.50
Total phospholipid	42.50	5.5-11.0	41.50	7.0-10.0	37.10
Sphingomyelin	32.70	0.7-1.0	9.35	0.6-0.8	25.90
Saponifiable phospholipid (Cephalin)	—	—	—	—	—
(Lecithin)	—	—	—	—	—
Total fatty acid	—	—	—	—	—
Neutral fat	—	—	—	—	—
Cerebrosides	—	—	—	—	—

visceral organs of patients with Gaucher's disease are not, as was formerly believed, galactosidocerebrosides but consist entirely of glucosidocerebrosides In 3 cases of Gaucher's disease examined in our laboratory, 2 showed only glucosidocerebrosides, 8.3 and 11.3 per cent respectively, and 1 contained 7.2 per cent glucosidocerebrosides and 8.6 per cent galactosidocerebrosides<sup>37</sup> In the infantile form of Gaucher's disease, in contrast to the adult form, only the galactoside variety of cerebrosides is found in increased concentration in the organs<sup>42</sup> Up to the present only this one case of infantile Gaucher's disease has been examined for the variety of cerebrosides\*

CHOLESTEROL AND ITS ESTERS

One should consider three different possibilities for the etiology of cholesterosis in cells and tissues cholesterol infiltration into the cell, a process that results from an accumulation of cholesterol and cholesterol esters in the serum (hypercholesteremia), cholesterol accumulation and retention within the

of these patients The figures resulting from the quantitative analysis of lipids in serum are characteristic of three different groups of xanthomatous disease and hence of great value for their differential diagnosis

A high serum cholesterol, a normal cholesterol/cholesterol ester ratio, a moderately increased lecithin in the serum but a normal serum value for neutral fat (serum is transparent) are found in essential xanthomatosis of the hypercholesteremic type (hypercholesteremic familial xanthomatosis) Characteristic of this group are tuberous or planar xanthomas of the skin (similar to yellow carotene in color), xanthomas of tendons, atheroma formation in the intima of blood vessels and of the endocardial lining of the heart and xanthomas of the lining of bile ducts

Normal cholesterol, lecithin and neutral-fat values of serum are observed in essential xanthomatosis of the normocholesteremic type (normocholesteremic xanthomatosis — synonymous with eosinophilic granuloma, Schüller-Christian syndrome and eosinophilic xanthomatous granuloma) The organs involved in this syndrome — singly, in various

\*In the meantime examination of the organs of the patient's brother showed glucosidocerebrosides and galactosidocerebrosides

combinations or generalized—are the skin (disseminated type of skin xanthoma), osseous system, dura, brain, lungs, pleura, lymph nodes and spleen.

Enormously increased values of neutral fat (milky or creamy serum) but only moderately increased values of cholesterol and lecithin are characteristic of idiopathic hyperlipemia with secondary eruptive xanthomas and of related syndromes in which severe hyperlipemia is the primary cause. Parallel with the degree of hyperlipemia, inflammatory skin xanthomas appear and disappear. In visceral organs only a few scattered foam cells may be found.

#### *Hypercholesteremia and Xanthoma Formation*

The concentration of cholesterol in the serum seems to depend on many factors. Some of the possible causes of hypercholesteremia and xanthoma formation are discussed below.

*Diminished destruction.* Thus far, no enzyme capable of splitting the terpen-like ring of cholesterol

ments<sup>51-54</sup> In these experiments cholesterol was determined as cholesterol-digtonid. From the fact that the expected amount of cholesterol did not precipitate with digitonin it cannot be concluded that the cholesterol skeleton was destroyed in the intermediary metabolism. The sterol nucleus may well have been intact, whereas oxidative or reductive changes may have resulted in a sterol unprecipitable with digitonin or not giving the Liebermann-Burchard test. Since it has been shown that bacteria present in the intestinal tract transform cholesterol to a sterol not precipitable by digitonin,<sup>57, 58</sup> it may be concluded that the deficit of cholesterol in balance experiments in animals, as well as in man, is due to a bacterial action on cholesterol in the intestines rather than to a disintegration of the sterol ring in the intermediary metabolism. On the basis of present knowledge an accumulation of cholesterol in the blood serum or in the tissues cannot be explained by a diminished

TABLE 2 (Continued)

LIPID	NORMAL LIVER	BRAIN IN NIEMANN-PICK DISEASE	NORMAL BRAIN	SERUM IN NIEMANN-PICK DISEASE	NORMAL SERUM	ARCTIC FLUID
	% of dried tissue	% of dried tissue	% of dried tissue	mg/100 cc	mg/100 cc	mg/100 cc
Total cholesterol	2.0-2.6	6.45	7.3-15.0	196	150-160	71
Free cholesterol	0.4-0.5	5.43	1.3-4.6	41	40-70	17
Cholesterol esters	1.5-2	1.0	6.1-10.3	62*	70-75*	56*
Total phospholipid	0.0-11.0	61.00	25.0-35.0	278	150-250	90
Sphingomyelin	0.3-0.5	4.84	4.5-7.0	24	10-30	—
Saponifiable phospholipid	—	—	—	254	110-230	90
(Cephalin)	—	—	—	(8)	—	(34.7)
(Lecithin)	—	—	—	(246)	—	(55.3)
Total fatty acid	—	—	—	614	200-450	130
Neutral fat	—	—	—	322	0-150	82
Cerebrosides	—	—	—	0	0	—

\*Per cent of total cholesterol

has been isolated from mammalian tissues. The chemical changes that occur in the intermediary metabolism of the cholesterol molecule take place in the side chain of that molecule, such as esterification of the alcoholic hydroxyl group, hydrogenation and oxidation of the sterol ring as well as of the side chain. It is not definitely known whether the sterol sex hormones are metabolites of cholesterol or the result of sterol synthesis, notwithstanding the fact that pregnanediol glycuronate containing deuterium was isolated from the urine of a pregnant woman after feeding of deuterium containing cholesterol.<sup>48</sup> Cholesterol derivatives in minimal quantities have been isolated from animal organs. It was suggested that cholestenone was present in deposits of cholesterol in the arterial wall.<sup>46, 47</sup> Hydrocholesterol has been isolated from the liver and from the serum of pregnant mares.<sup>48</sup> Dicholesteryl ether is present in the spinal cord of the ox.<sup>49</sup> Cholestenone is produced by the action of proactinomyces on cholesterol.<sup>50</sup>

A destruction of the cholesterol skeleton was concluded from negative cholesterol balance experi-

ments of the sterol ring in the intermediary metabolism.

*Increased formation.* As stated above, enzymes capable of splitting the sterol skeleton are not known to be active in the intermediary and cellular metabolism of animals. Consequently, an accumulation of cholesterol due to an intracellular enzymatic disturbance is not likely to be the result of a decreased cholesterol catabolism but rather of an increased anabolism—that is, increased synthesis of cholesterol. Earlier investigations of cholesterol metabolism have shown that the sterol-ring system is constantly synthesized in the mammalian organism.<sup>43, 49-51</sup> Schoenheimer,<sup>52</sup> by the administration of materials containing deuterium, demonstrated that the small molecules of two and three carbon atoms, which may be derived from all three food constituents (protein, carbohydrates and fats) are the basis of cellular sterol synthesis. Macleod and Smedley-MacLean<sup>53</sup> had already shown in 1938, by the use of acetic acid labeled with deuterium, that yeast is able to synthesize more than 50 per cent of its cholesterol from acetic acid. Bloch,<sup>54, 55</sup> in 1942,



employing labeled acetic acid in experiments with rat-liver slices, also demonstrated that considerable quantities of cholesterol are synthesized from acetic acid in the liver. The question that arises is, Which organs and cells are capable of cholesterol synthesis? Even if there is no definite answer, it is probable that every growing cell during maturation is capable of synthesizing cholesterol. This function in later life seems to be maintained in rapidly proliferating histiocytes and reticulum cells in certain disorders in which the functional capacities of embryonal cells—especially embryonal fat cells—to form all kinds of lipids are apparently preserved<sup>66, 67</sup>. In the fully developed organism the liver apparently plays a special part not only in the excretion but also in the synthesis of sterols. The experiments of Thannhauser, Enderlen and Jenke<sup>68</sup> on dogs with bile fistulas demonstrated that the synthesis of the sterol skeleton of bile acids occurs as a biologic synthesis in the liver. In further experiments it was shown that after liver extirpation in dogs the serum cholesterol is not considerably decreased after twenty-four hours<sup>69</sup>. The lowest cholesterol values, however, are observed in the serum of patients with acute yellow atrophy of the liver<sup>70</sup>. This observation supports the theory that the liver plays an important role in the formation of cholesterol in the mature organism. Different clinical manifestations may occur whether the increase of cholesterol formation takes place in or outside the liver. It may be suggested that the clinical syndrome designated by Thannhauser and Magendantz<sup>43</sup> as "primary essential xanthomatosis of the hypercholesteremic type"—with hypercholesteremia, hyperlecithemia but normal neutral fat content of the serum as the leading clinical signs—is the result of increased cholesterol and lecithin formation in the organism, possibly in the liver. The exact site of the increased formation of cholesterol, however, has not yet been ascertained.

This syndrome (hypercholesteremic familial xanthomatosis) is characterized by xanthoma formation in the skin (plain and tuberous xanthomas), xanthomas of the tendons, in which the nodules consist of cholesterol-containing foam cells and fibrous tissue, and xanthoma of the intima of the blood vessels and of the endocardial lining of the heart. The incidence of this syndrome in families as a recessive hereditary stigma is of great interest. The complete syndrome may be present in members of the same family, whereas in others only hypercholesteremia may be found—the incomplete form or *forme fruste*<sup>43, 71, 72</sup>.

**Increased formation in the liver and impaired excretion.** An imbalance of cholesterol formation and excretion is suggested as the cause of xanthomatous biliary cirrhosis, a syndrome that is characterized by the following clinical symptoms: skin xanthomas of the plain and tuberous variety, enlarged liver and spleen, obstructive type of jaundice of years' dura-

tion, extremely high values for total cholesterol (increased four to six times normal) and extremely high values for lecithin (increased four to eight times normal), transparent serum and diminished values for neutral fat in the serum despite the outstanding increase of cholesterol and lecithin<sup>43, 73-76</sup>.

On the basis of newer anatomic observations Thannhauser<sup>73</sup> has reconsidered his previous opinion concerning xanthomatous biliary cirrhosis and now suggests that the imbalance of cholesterol and lecithin formation and excretion is at the outset a functional disturbance of the liver<sup>77</sup>. In later phases anatomic changes in the bile capillaries (cholangioles) lead to a special type of biliary cirrhosis<sup>1</sup>. MacMahon and Thannhauser<sup>78</sup> in a study of the livers of 5 patients showing the typical clinical signs of xanthomatous biliary cirrhosis, as described above, found in the early stages a nonspecific chronic inflammatory reaction centered about the smallest bile ducts and junction ducts of the portal areas. There was blocking of the ducts and subsequent intralobular bile stasis. The larger bile ducts were patent and free.

Xanthomatous biliary cirrhosis is an independent clinical syndrome, occurring together with plain and tuberous xanthomas of the skin, xanthoma formation in the intima of the blood vessels and the endocardial lining of the heart and xanthomas in the lining of the bile ducts. In contrast to previous opinion, the xanthoma formation in the lining of the bile ducts, with resulting obstruction, is not considered the cause of xanthomatous biliary cirrhosis, since it was not found in 3 cases at autopsy<sup>78</sup>. For this reason it is believed that xanthoma formation in the lining of the bile duct may occur in rare cases, similar to atheroma formation in arteries, as one of the possible features of but not as the cause of the disease.

**Impaired excretion due to hepatitis.** In almost all cases of epidemic hepatitis or of toxic hepatitis in its acute or chronic stages, the total cholesterol in the serum is increased. The value of cholesterol present as esters in the serum (normally 70 to 75 per cent of the total cholesterol) decreases in proportion to the severity of the acute liver-cell damage. During convalescence the total cholesterol, as well as the cholesterol present as esters, gradually returns to normal. In chronic hepatitis the values for the total cholesterol are slightly increased, whereas the cholesterol present as esters remains low. In acute yellow atrophy of the liver the total cholesterol is below normal, signifying that insufficient functioning liver parenchyma remains for cholesterol synthesis. In these cases the lowest cholesterol values are observed<sup>70</sup>.

**Mechanical obstruction of common bile duct.** This condition, due to stone, inflammation or tumor, results in a retention of all bile constituents and consequently of cholesterol. The serum of patients

\*Pericholangiolitic biliary cirrhosis

suffering from mechanical obstruction of bile ducts does not usually show extremely high cholesterol figures (one or two times normal). The ratio of cholesterol to cholesterol present as esters is altered only if acute or chronic damage of the liver cells accompanies the mechanical obstruction.<sup>70-72</sup>

Hypercholesteremia of greater degree (three or four times normal) may develop after injury of the common bile duct during an operation resulting in its complete obliteration. Notwithstanding complete obstruction of long duration, skin xanthomas usually do not develop. The occurrence of secondary xanthomas has been reported only rarely, and these have disappeared after the patency of the common duct has been restored.<sup>73</sup>

**Hyperlipemia** The cholesterol content of the blood serum may be increased without functional or mechanical impairment of cholesterol excretion in cases in which hyperlipemia (creamy serum) occurs. Hyperlipemia may be due to an increased transportation or diminished deposition of neutral fat, as pointed out above. Whenever neutral fat increases in the serum, cholesterol accompanies the neutral fat and results in an increase of free cholesterol and cholesterol esters. In such cases foam cells are caused by an increased uptake of fat and cholesterol from the serum (cholesterol infiltration) and are observed especially in the skin and to a minor degree scattered in the spleen, liver and lungs.

The clinical syndromes in which xanthoma formation secondary to hyperlipemia may be encountered are as follows: idiopathic hyperlipemia with secondary xanthomatosis (slight diabetes may or may not be present, the hyperlipemia and xanthomas disappear after neutral fat is restricted in the diet, insulin is not effective in the treatment of hyperlipemia in these cases)<sup>68</sup>, hyperlipemia with secondary xanthomatosis due to untreated severe diabetes mellitus<sup>69</sup> (insulin treatment alone corrects the diabetic condition as well as the hyperlipemia, and the xanthomatous eruption consequently disappears), idiopathic familial hyperlipemia<sup>74-76</sup> (these cases are favorably influenced by a diet low in fat, the hyperlipemia never completely disappears but is considerably reduced), idiopathic hyperlipemia, hepatosplenomegaly and secondary xanthomatosis with hepatosplenomegaly of the Bürger-Grütz type<sup>6</sup> (this is probably a variation of the syndrome, idiopathic hyperlipemia), hyperlipemia in chronic pancreatitis (this may cause secondary xanthoma formation in rare cases<sup>10-12</sup>), and hyperlipemia in severe cases of glycogen-storage (von Gierke's) disease (the occurrence of secondary xanthoma in this disorder is rare<sup>13-15</sup>).

**Hypothyroidism** In cases of hypothyroidism the cholesterol content of the serum is elevated. The reason for this increase is not known. Thyroid medication reduces the cholesterol level of the serum in these patients. In rare cases of hypothyroidism with high serum cholesterol levels, foam

cells with xanthoma formation may be found in the skin.<sup>68</sup> Neutral fat and total phospholipids are not increased or show only a slight rise.<sup>68</sup> In hyperthyroidism the total cholesterol level in the serum is a low normal or sometimes below normal. The cholesterol-cholesterol ester ratio in hypothyroidism and hyperthyroidism is normal.

(To be concluded)

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CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*BENJAMIN CASTLEMAN, M.D., *Associate Editor*EDITH E. PARRIS, *Assistant Editor*

## CASE 33401

## PRESENTATION OF CASE

A thirty-year-old housewife entered the hospital because of shortness of breath and a mass on the chest wall.

The patient had experienced episodes of dyspnea with emotional stress for three years. A year before admission she had been seen in the Out Patient Department, and the dyspnea was thought to be due to an anxiety state. No mass was noted at that time, although the patient stated that she had first noted it following a fall eighteen months before admission. The mass continued to grow and became tender. She noted weakness for several months and lost 5 to 10 pounds. A month before admission she was seen at another hospital, where a mass was observed over the left seventh rib anteriorly and bloody fluid was removed from the left pleural space. For three days prior to admission she had chills and fever.

Physical examination revealed an acutely ill woman perspiring freely. Over the left seventh rib anteriorly near the costal margin was an extremely tender, hard, fixed mass 6 by 4 by 3 cm. The left side of the chest was flat to percussion, with absent breath sounds posteriorly on the left.

The temperature was 99.6°F, the pulse 100, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

The urine had a specific gravity of 1.014 and contained no albumin, and only rare white cells and granular casts were observed in the sediment. Examination of the blood revealed a red-cell count of 3,200,000, with 11 gm. of hemoglobin, and a white-cell count of 11,500. The total protein was 6.3 gm. per 100 cc.

On the first hospital day 100 cc. of serosanguineous fluid was removed from the left pleural cavity. The specific gravity was 1.022. On smear no tumor cells were seen. An x-ray film of the chest following the tap showed fluid in the left pleural cavity forming a fluid level opposite the tenth vertebral body posteriorly. A moderate pneumothorax was present on the left. The heart and mediastinum were dis-

placed to the right. The left lower lobe was collapsed. There was mottling of the bone structure of the anterior portion of the seventh rib with some new-bone formation.

On the second hospital day an operation was performed.

## DIFFERENTIAL DIAGNOSIS

DR. CLIFFORD C. FRANSEEN. The significant findings from which we may get some leads are: the age of the patient (thirty years), the duration of the symptoms, — there is some question whether it was three years or eighteen months before admission, when she had the fall, that she first noticed the mass, — the slight fever, the extremely tender character of the mass on the chest wall, the probable secondary anemia, the elevation of the white-cell count, the exudative character of the pleural fluid that was removed and the fact that the lesion in the rib showed bone destruction and some new-bone formation. In every case of this kind, with a lesion in the bone, we have repeatedly emphasized the importance of reviewing the case from several aspects. In the first place, is it a neoplasm, and if it is neoplastic, is it primary or metastatic? If primary, is it benign or malignant? Then, is it an inflammatory or granulomatous lesion, or does it have a metabolic basis? One by one, we try to exclude these possibilities and to arrive at some conclusion regarding the character of the lesion.

When this patient was seen a year previously in the Out Patient Department no mention was made of an x-ray examination. Of course, that was the time to take an x-ray film. The patient had been aware of the mass six months previously. This lesion might have been discovered at that time.

If we consider neoplasm, was it primary? It could have been primary in the rib or perhaps, from this description, in the pleura, and there is a remote possibility that it was in the lung. Primary tumors of the pleura are quite rare, of course. Secondary invasion of the rib or destruction of the rib, from a pleural tumor, is not common, and altogether the picture does not fit too well with primary tumor of the pleura. Among the tumors of the pleura, the so-called "endotheliomas" are the most frequent. They may produce pleural effusion, but usually not of such a high specific gravity as the tumor in this case showed.

The primary tumors of the rib must, of course, be considered more seriously. It might be well to look at the x-ray films, because they are important in a case of this nature.

DR. STANLEY M. WYMAN. The films, taken six days apart, show fluid in the left pleural cavity with a small amount of air above. The rib detail is unsatisfactory in the first two films but suggests on the later films some mottling and destruction in the body of the rib. The distal 5 or 7 cm. of the rib shows multiple destructive areas in the body of the

medulla, with some periosteal reaction. There is slight bone reaction with increased density in the rib.

DR. FRANSEEN: Is there any expansion of the cortex?

DR. WYMAN: It does not appear to be expanded.

DR. FRANSEEN: So far as the x-ray studies are concerned the important findings include a bone-destructive lesion that is producing new bone. Among the primary tumors of the rib one must consider almost the entire field. Osteogenic sarcoma of the rib, of course, is quite rare. In this group, the chondrosarcomas are more frequent. They can, of course, be osteoplastic and produce new bone, but my impression is that the new-bone formation would be of a different type than that seen in the case under discussion, which is somewhat irregularly distributed. Multiple myeloma is a fairly common tumor of the rib, but it is a purely destructive lesion, almost without exception, and it does not form new bone. Pathologic fractures in these latter lesions are very common, but there is no fracture here or thinning to any extent. Hodgkin's disease, in particular, may affect the rib but usually in the late stages of the disease, and we have no real evidence for including that lesion.

Ewing tumor is not an uncommon lesion at this site and may produce new-bone formation with effusion into the chest cavity. I do not see how one can entirely exclude that possibility.

Metastatic lesions of the rib are perhaps the most frequent statistically. This patient was a relatively young woman, and we have no evidence for considering a metastatic lesion on the basis of the data provided us. Metastatic lesions of this type usually do not produce new bone in a rib.

We must consider inflammatory lesions seriously because of the extremely tender character of the mass, the slight fever and some leukocytosis. Many of the slowly developing, inflammatory lesions of bone can produce both bone destruction and new-bone formation. Some of the granulomatous types, like syphilis, might be considered, and although no serologic findings are reported, there is no reason for considering syphilis seriously. I mention it because almost all bone tumors may on occasion be simulated by syphilis or by tuberculosis, which can perhaps also be excluded.

We then come to a consideration of chronic osteomyelitis. This must have been a relatively chronic process, with an acute episode toward the end, with chills and fever and with exudate in the pleural cavity. We know that chronic osteomyelitis may persist in bones like this for a long time with relatively little reaction. The patient had a fall with apparent injury at that site, although not necessarily, because after a fall people feel themselves all over and discover masses that were present prior to the injury. Women, particularly, are apt to discover

masses in the breast under such circumstances and to say that the mass was due to a fall.

There are diseases such as eosinophilic granulomas of the rib, which are quite rare, and I am not familiar with all the variants that can occur in them because of the paucity of cases that have been recorded. Whether it can simulate this lesion, I am not prepared to say. A biopsy would be necessary to establish these diagnoses.

So far as metabolic lesions go, we have nothing in the report to suggest that this lesion had a metabolic basis. The only blood chemical finding reported is the total protein, which was not remarkable. The determination is important, of course, in the consideration of multiple myeloma, in which it is almost always elevated.

In putting all these facts together we find that the duration was relatively long for a malignant process in the rib. If it were a malignant tumor, it would have to be relatively slowly growing. I cannot escape the impression that this was an inflammatory lesion—probably some form of chronic osteomyelitis with late pleural effusion. The fluid may have been present for a longer time, but it was the pleural reaction that brought the patient to the hospital. I had to choose among these various diagnoses, should put osteomyelitis first, but with the reservation that many of the other lesions that I have mentioned cannot be excluded except by biopsy.

#### CLINICAL DIAGNOSIS

Ewing tumor?

DR. FRANSEEN'S DIAGNOSIS

Chronic osteomyelitis of rib

#### ANATOMICAL DIAGNOSIS

*Ewing tumor of rib and phalanx of toe.*

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: This lesion was first aspirated with a large needle, and all that could be removed was some connective tissue in which there were a few deeply stained cells that we could not make anything of. They were apparently traumatized in the aspiration biopsy, and we believed that the biopsy was inadequate to make a diagnosis. The patient was then admitted to the hospital, and an open biopsy performed, which showed a Ewing tumor of a rather typical form, but without, at least in our biopsy, any evidence of reaction.

A week after the biopsy the right fourth toe became painful and swollen. The patient stated that this had occurred intermittently for about a year. An x-ray film was taken, and Dr. Wyman will show the films.

DR. STANLEY M. WYMAN: The proximal phalanx of the fourth toe shows multiple rather cyst-like areas that are, however, very ill-defined but somewhat indicative of destruction. There is a slight suggestion of a little periosteal reaction.

Dr CASTLEMAN Will you discuss the lesion in the toe, Dr Franseen?

Dr FRANSEEN It is unfortunate that the patient did not have this four days earlier because with a multiplicity of lesions, I should have been more willing to accept a diagnosis of Ewing tumor. We know that Ewing tumor, more frequently than any other bone tumor, produces a response suggestive of inflammation in these various sites, and the appearance of this additional lesion would be entirely consistent with it.

Dr CASTLEMAN Have you ever seen metastases of Ewing tumor in the phalanges?

Dr FRANSEEN I do not remember that I have seen one.

Dr WYMAN I think that they are extremely rare, but I believe that we have seen one.

From the x-ray films I should not have thought that the lesion in the toes was Ewing tumor. The radiograph is consistent with it, but the toe is an unusual location.

Dr FRANSEEN I should certainly not be able to make a diagnosis from this x-ray film of the toe.

Dr CASTLEMAN The toe was amputated and also proved to contain a Ewing tumor. I believe that it is the first one we have seen in this location. Geschickter\* mentions a few in the tarsus and metatarsus but none in the phalanx. The fact that no lesions are seen on the films of the other bones raises the remote possibility that the toe lesion was another primary tumor. The chances are, however, that this is the first of other metastases that will become evident later. The patient is receiving x-ray treatment over the rib.

\*Geschickter, C. F. and Copeland, M. M. Tumors of bone. *J. Intern. Med.* 1933 343 1930.

## CASE 33402

### PRESENTATION OF CASE

A fifty-four-year-old married woman entered the hospital with the complaint of lower abdominal cramps of two days' duration.

The present illness began abruptly about forty-eight hours before admission. There were severe lower abdominal cramps with continuous aching and a sense of fullness. The patient was nauseated and vomited several times without relief. There was no change in bowel habit, and no urinary symptoms were noted. She felt feverish but had no chills. She was seen by a physician, who noted a mass in the lower abdomen. Pelvic examination revealed a firm, somewhat movable and tender tumor about the size of an orange occupying the apex of the vagina in the region of the cervix, no other mass could be felt. The pain was relieved temporarily by morphine but recurred. Hospitalization was advised.

The patient's health had always been excellent. An appendectomy had been performed twenty-seven years before admission. The menstrual history was normal. She had had two children without complication. Two years before admission the menstrual periods had ceased. There was moderate annoyance from hot flashes and sweats, and she had severe mental depression. These symptoms were relieved by estrogens, and some form of hormone therapy had been administered up to the time of admission to the hospital. Approximately four months before admission conization of the cervix was carried out to relieve a complaint of vaginal discharge.

Physical examination disclosed a flushed and somewhat dehydrated woman in some distress. The abdomen was soft, and peristalsis was normal. There were tenderness and a sense of an asymmetrical mass in the suprapubic area. Pelvic examination was essentially as described above.

The temperature was 99.4°F, and the pulse and respirations were normal. Examination of the blood revealed a hemoglobin of 11.6 gm and a white-cell count of 8700. A catheter specimen of urine showed no albumin or sugar, the sediment contained rare red cells and 12 white cells per high-power field. Cytologic examination of the vaginal secretion was negative.

There was no change in the patient's condition overnight. On the day following admission an operation was performed.

### DIFFERENTIAL DIAGNOSIS

Dr FRANCIS M. INGERSOLL The tender, movable mass occupying the apex of the vagina must have accounted for the symptoms of the low abdominal cramps and a sense of fullness. The description of the pelvic examination failed to note if the cervix was present in addition to the mass or whether this mass was actually the cervix. No mention was made of the size, shape or position of the uterus, although a symmetrical mass in the suprapubic area was described. The uterus and cervix must have been present, since the only previous operation was an appendectomy. To arrive at a diagnosis in this case it is necessary only to decide what the mass in the pelvis was.

This mass seemed to be so close to the vagina that an ovarian tumor can probably be ruled out. If the patient had had a previous total hysterectomy the mass could have been an ovarian tumor adherent to the vaginal apex, but since the uterus was apparently still present, ovarian tumors could not have occupied this position.

A vaginal cyst or tumor displacing the cervix and uterus is a possibility. Gartner's duct—a tube that is the homologue of the vas deferens, and a relic of the embryonic wolffian duct—occasionally causes cystic masses in the vagina, but they are usually on the lateral vaginal wall, rarely cause pain and

should have been discovered at the conization operation four months previously. Inflammatory masses are ruled out by the lack of fever and the normal white-cell count.

The field is narrowed down, then, to some lesion of the cervix itself. Cervical fibroids sometimes distort the entire organ and may become orange sized, but the patient was fifty-four years of age and fibroids do not develop in that age group, since it must be assumed that they were not present four months previously.

An enormous Nabothian cyst might feel like this tumor at the apex of the vagina. These cysts are unlikely to reach such a size. Moreover, two facts in the history can be correlated to account for this mass in the vagina: the patient had had a conization of the cervix, and she had been taking estrogens for hot flashes and mental depression. A common occurrence after estrogen therapy is uterine bleeding. No mention of any postmenopausal bleeding is found in the record. A frequent complication following conization of the cervix is stenosis of the cervical canal, with trapping of blood in the uterus. A distention of the cervical and endometrial canals occurs, causing pain and a sense of fullness in the pelvis. This diagnosis of cervical occlusion with distention of the cervical and endometrial canals with blood best explains the clinical picture in this case.

#### CLINICAL DIAGNOSIS

Hematometrium due to cervical stenosis

#### DR INGERSOLL'S DIAGNOSIS

Hematometrium due to cervical stenosis

#### ANATOMICAL DIAGNOSES

*Hematometrium due to cervical stenosis*

Adenomyosis of uterus

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN: Will you tell us what was found at operation, Dr Ulfelder?

DR HOWARD ULFELDER: Under anesthesia one could easily feel a movable, smooth, rounded pelvic tumor about the size of a grapefruit. It was palpable

in the suprapubic region and presented at the apex of the vagina as a fluctuant, rounded surface with no sign of the cervix. One small dimple suggested the external os. A needle inserted here aspirated dark blood. The opening was enlarged, and free drainage allowed for a large hematometrium.

Eight days later an abdominal hysterectomy was performed. The uterus had shrunk to normal contour and was easily removed, together with the cervix.

DR CASTLEMAN: On opening the specimen it was apparent that the cervix was markedly constricted at the external os and had been greatly expanded and thinned out by the accumulation of secretions and blood. The fundus had been only slightly involved and had risen on top of the expanding cervix. Microscopically, the area of stenosis showed only chronic inflammation. The myometrium was extensively involved with adenomyosis.

DR ULFELDER: Stenosis of the cervix following by hematometrium or pyometrium is a complication not infrequently seen after application of radium or cauterization. It may occur without antecedent trauma as a result of menopause atrophy alone. This is particularly true in patients in whom estrogen bleeding is induced after years of inactivity. Dr Ingersoll has emphasized the point that a combination of trauma to the cervical canal and uterine bleeding due to estrogens is the most frequent history in these cases. The usual site of stricture is at the internal os, since the canal is narrowest at this point, and in such cases a dilated and thinned uterine body with an undistorted cervix is still found to be present in the usual position. Occlusion at the external os, as in the case under discussion, is rare.

Although adequate drainage is easily established, two points must be kept in mind during the treatment of this condition: cancer as the cause of obstruction must be excluded, and there is a tendency for the inflammatory stenosis to recur if the uterus is not removed. If hysterectomy is not planned, a rubber T-tube catheter should be left in the fundus with the long arm out through the cervical orifice for at least three months, until a permanent channel can be established.

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## RED CROSS NATIONAL BLOOD PROGRAM

THE plans of the American Red Cross to administer and finance a program designed to provide, without charge, blood and its derivatives for all the people of the United States\* is a fitting climax to the magnificent job done by this organization during the war. The extent of the program is indicated by the estimates that, eventually, about four million pints of blood will be needed annually and that nearly \$20,000,000 will be required each year to cover all costs. The great value of blood and its derivatives in the saving of human lives has been proved, particularly during the war, and there can be no doubt that a national enterprise of this sort is badly needed. Nor is there any question that the American Red Cross, which supplied more than

thirteen million pints of blood to the armed forces, is best qualified to undertake this gigantic effort as a peace-time service.

Four distinct phases are involved in the program: collection of the blood, its processing, packaging and storage, its distribution, and continuous research and investigation of the quality of the products and their proper usage. In addition to whole blood, the following derivatives will be provided: plasma serum albumin, immune serum globulin, anti-hemophilic globulin, blood-grouping serums, fibrin films and red-cell suspensions, paste and powder. Other products will undoubtedly be made available as soon as their usefulness in medicine and surgery has been proved. Under the guidance of the national organization, the general plan of operation will be handled by the Red Cross chapters, which will work in co-operation with the medical societies, public-health agencies, hospitals and other institutions in their communities.

It is expected that state or community programs already established will be given a further impetus through integration with the national endeavor to provide a greater variety of blood derivatives. In Massachusetts the burden of establishing such a program has been largely borne by the Department of Public Health and hospital and medical groups, the role of the Red Cross having been that of donor procurement and certain nontechnical local assistance. With the undertaking of a blood program as a major activity of the American Red Cross it may be possible to extend the program in Massachusetts, which, with the limited funds at present available, has never been able to catch up with the ever-growing requirements for blood and blood products in the Commonwealth.

A program such as this demands constant support of all concerned with it — as physicians or patients or in other capacities. The only way of ensuring the success that the endeavor must achieve if the needs for blood are to be met is for all concerned to give active aid and encouragement to every effort designed to make more blood available.

To put this program in operation in all sections of the United States will be difficult and will require time. But the benefits that will accrue are incalculable: there is no means of measuring the value

\*McGrath G. F. National blood program inaugurated. *Red Cross Courier* 27:3 (July) 1947.



of the lives that will be saved and the suffering that will be alleviated by the immediate provision of blood and its derivatives, without cost, to the ill and injured. It is a typical undertaking of the American Red Cross in its goal to be of service to humanity, and it deserves enthusiastic and wholehearted support by all.

## EPIDEMIOLOGY OF NEONATAL SKIN INFECTION

A RECENT paper by Allison and Hobbs\* presents an interesting study on the epidemiology of pemphigus neonatorum. This investigation, conducted between November, 1943, and November, 1945, in the nursery of a maternity unit in Cardiff, Wales, was occasioned by a recent considerable increase in the infection, particularly in the nurseries of this and similar obstetric hospitals.

During the period of the investigation 2719 infants were born in or admitted to the hospital, of these, 111 (4.1 per cent) developed pemphigus. In addition, 25 cases of staphylococcal conjunctivitis occurred, either alone or in association with the pemphigus.

It is notoriously difficult to trace staphylococcal migrations on account of the varieties of strains and the ubiquity of the organisms. The study was nevertheless attempted, painstakingly and meticulously, with culturing of the lesions, the noses, the eyes and, in some cases, the umbilici of the infants, of the noses and the throats of the mothers, doctors, attendants and nurserymaids, of the air and the dust of the nursery, and of the blankets and the gowns. The infecting organism, a coagulase-positive staphylococcus, frequently in pure culture, was obtained from every lesion investigated, and the strains were checked serologically. A low correlation was found between mothers and infants: rarely a mother developed a sore throat, apparently from her infected infant, and the converse was never noted. But the organism was found to be widespread in the infants' environment, being recovered from the noses and throats of some of the healthy infants, from the blankets, gowns, dust and air and particularly, from a high proportion of the noses of

\*Allison, V. D., and Hobbs, B. C. Inquiry into epidemiology of pemphigus neonatorum. *Brit. M. J.* 2 1-7, 1947.

the nursing staff. It must be admitted that nursery conditions during most of the period of the study were not good, since the nursery was badly overcrowded, as well as poorly lighted and ventilated because of air-raid precautions.

The implications of this study are obvious, and they give added emphasis to knowledge already possessed regarding discharges from the human nasopharynx. These constitute a significant, if not the most important, source of staphylococcal, streptococcal and other infections of this type, and the carrier, regardless of the precautions taken, has no place in an infant nursery or surgical operating room or ward or, indeed, in any manner of close contact with other persons. No great imagination is necessary to conjure up a number of links in the chain of infection—the iniquitous pocket handkerchief, with hands unwashed after its use, the popular swimming pool or bathing pond and the family toothbrush holder.

In the nursery nothing can take the place of adequately developed consciences and a technique that has become automatic through intensive training. This study introduces further evidence in favor of the isolated mother-infant unit in maternity departments.

## MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

### DEATHS

POTTER — Lester F. Potter, M.D., of New Bedford, died on August 17. He was in his seventy-fifth year. Dr. Potter received his degree from Bowdoin Medical School in 1897. He was a member of the New England Otological and Laryngological Society.

SHATSWELL — James A. Shatswell, M.D., of Beverly, died on August 26. He was in his eighty-fourth year. Dr. Shatswell received his degree from College of Physicians and Surgeons of Baltimore in 1890. His widow and a brother survive.

SPIEGL — Erwin D. Spiegl, M.D., of Lynn, died on April 6. He was in his forty-sixth year. Dr. Spiegl received his degree from Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, in 1923. He was a member of the staff of the Lynn Hospital.

# MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	Oct. 6	Paul W. Hugenberger
Brockton	Oct. 9	George W. Van Gorder
Gardner (Worcester Subclinic)	Oct. 14	John W. O'Neara
Pittsfield	Oct. 15	Frank A. Slowick
Worcester	Oct. 17	John W. O'Neara
Greenfield	Oct. 20	Charles L. Sturdevant
Springfield	Oct. 21	Garry deN. Hough, Jr.
Hyanis	Oct. 23	Paul L. Norton
Fall River	Oct. 27	David S. Grace

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments.

## BOOK REVIEWS

*The Journals and Letters of the Little Locksmith* By Katherine B. Hathaway 8, cloth 395 pp., with 17 illustrations by the author. New York: Howard-MacCann, Incorporated 1946. \$3.75.

Anyone who is interested in psychiatry will find this book revealing, and if the reader is concerned with the psychology of literary artists, he may find it doubly interesting. It presents the intimate story of a remarkable life spent struggling first with a severe deformity of the spine and then with the host of secondary problems that resulted from being "The Little Locksmith," which was the way in which the author chose to think of her disability. The psychological benefits from the illness compensated only partly for the original injury to her personality, and these compensations in turn led to complicated emotional situations which she describes in this book with unusual skill and some insight. She records her sensitive reactions and displays dynamic patterns in her behavior so carefully that the perceptive reader will be well repaid for the time he spends on the book.

One must read *The Little Locksmith*, an earlier book by the same author, to appreciate the full power and courage of this extraordinary woman, who in some ways resembles Katherine Mansfield, although Katherine Hathaway had more to endure in the way of physical hardship. The setting of her story is Salem, Massachusetts, but it also takes in Cambridge and Boston of course as well as Maine and travel in Europe.

Miss Hathaway's whole life was spent more or less in the care of medical specialists from spine to soul straighteners. She lived first in a Bradford frame and then in a body brace for years. She had to take special exercises all her life, and could rest and work only in certain strained positions. In her younger days she had a psychoanalysis with Dr. Lettice DeForest, followed later by eclectic psychotherapy with Dr. Merrill Moore, who encouraged her in the writing of books. For the preservation and editing of her manuscripts credit is due her brother Warren H. Butler of Salem, who, serving effectively in the role of literary executor, has made her books available to the public. Katherine Hathaway died in the prison of her deformed body on Christmas Eve, 1942 just before her first book was published, with heart failure due to increasing restriction of the heart and lungs secondary to the spinal curvature. *The Little Locksmith* immediately became a literary success and a Book-of-the-Month Club choice. She was showered with posthumous literary recognition. Her legend, as one of America's most unique woman writers, is now growing to such an extent, particularly in New England literary circles, that she is already a myth and may become a cult in a small way especially among physically handicapped persons. Few people writing in recent years have recorded with such sincerity and vitality their innermost thoughts and few have left such an inspiring and beautiful documentation of their passage through life.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Clinical Allergy. A monograph on the management and treatment of allergic diseases.* By Alexander Sterling M.D. With the assistance of Bea Sterling Hollander M.D. 8<sup>th</sup>, cloth, 198 pp., with 16 illustrations. New York: International Universities Press 1947. \$5.00.

This manual discusses clinical allergic problems, especially from the viewpoint of diagnosis and therapy. The text is amplified with 51 case histories illustrative of various conditions. The price seems excessive for this small volume.

*Gynecology with a Section on Female Urology.* By Lawrence R. Wharton, Ph.D. M.D., assistant professor of gynecology, Johns Hopkins Medical School, assistant acting gynecologist, Johns Hopkins Hospital, and consultant in gynecology, Union Memorial Hospital Hospital for the Women of Maryland and Church Home and Infirmary. Second edition. 8<sup>th</sup>, cloth 1027 pp., with 479 illustrations. Philadelphia: W. B. Saunders Company 1947. \$10.00.

This second edition of a standard textbook, first published in 1943 has been revised to date. The sections on embryology and congenital malformations have been reorganized and rewritten. The technique of ureterotomy for ureteral stone has been amplified. A chapter on water cystoscopy, written by Dr. Charles L. Prince, has been added to the section on female urology, and a separate chapter has been devoted to the female urethra. New illustrations have been included in connection with new developments in operative technique.

## NOTICES

### ANNOUNCEMENT

Dr. Frank B. Colloten announces the removal of his office to 73 Bay State Road, Boston.

### JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston

Lecture Hall, 9-10 a.m.

### MEDICAL CONFERENCE PROGRAM

Wednesday, October 8 — The Pulmonary Segment as a Unit for Treatment. Dr. Richard H. Overholt.

Friday, October 10 — Pulmonary Embolism. Dr. Lewis Dexter.

Wednesday, October 15 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, October 17 — Gastritis. Dr. Seymour Gray.

Wednesday, October 22 — Uterine Retrodisplacements. Dr. George A. Bourgeois.

Friday, October 24 — Traumatic Shock. The physiologic effects of blood loss. Dr. F. A. Simeone.

Wednesday, October 29 — A Discussion of Clinical Otoliths with Demonstration of the Fenestration Operation. Dr. Philip E. Meltzer.

Friday, October 31 — Precautions in Handling Radioactive Materials in Medical Research. Dr. Shields Warren.

On Tuesday and Thursday mornings from 9:00 to 10:00 Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Friday afternoons from 2:00 to 4:00 therapeutic conferences will be held with round-table discussion. Dr. R. P. McCombs, Moderator. On the second and fourth Friday afternoons of each month Dr. Merrill Sosman will conduct x-ray conferences from 4:00 to 6:00. On Saturday mornings from 9:00 to 10:00, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the Staff from 12:00 to 1:00.

All exercises are open to the medical profession.

## NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the New Haven Hospital, New Haven, Connecticut, on Wednesday, October 8, at 2 00 p m The meeting is open only to members and invited guests

## HARVARD MEDICAL SOCIETY

The first meeting of the Harvard Medical Society will be held in the amphitheater of Building D, Harvard Medical School, on Tuesday, October 14, at 8 p m Members of the Biophysical Laboratory of Harvard Medical School will present a symposium entitled "Biological Problems Studied with Isotopes"

## PROGRAM

- Rates of Biological Processes in the Intact Animal Dr DeWitt Stetten, Jr  
Some Aspects of the Metabolism of Zinc as Studied with the Radioisotope  $Zn^{65}$  Drs John G Gibson, 2nd, and Bert L Vallee  
The Incorporation of Alanine into Protein Drs Ivan D Frantz, Jr, Robert B Loftfield and Warren W Miller  
Tracer Studies of Gas Exchange in Man Drs A C Barger and E M Landis  
Some Studies in Radioautographs Drs A K Solomon and J C Cobb

Subsequent meetings will be held on November 4 and December 19, 1947, and January 13, February 10, March 9, April 13 and May 11, 1948

## JOINT MEETING OF NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS AND AMERICAN SOCIETY OF ANESTHESIOLOGISTS, INCORPORATED

A joint meeting of the New England Society of Anesthesiologists and the American Society of Anesthesiologists, Incorporated, will be held in Boston on November 10

## PROGRAM

- 8 a m to 12 m Clinical demonstrations in operating rooms of the Massachusetts General Hospital, Massachusetts Memorial Hospitals, St Elizabeth's Hospital, New England Deaconess Hospital, New England Baptist Hospital and Boston City Hospital  
12 30 p m to 1 30 p m Informal luncheon at the Hotel Sheraton  
2 00 p m Scientific program at the Hotel Sheraton Dr Julia G Arrowood will speak on "Pain Mechanisms" Drs William H Sweet and William T Chapman will lead the discussion  
3 00 p m Dr L K Diamond will speak on the subject "Whole-Blood Transfusions and Untoward Reactions," which will be discussed by Dr C P Emerson  
7 00 p m Dinner at the Hotel Sheraton Dr B B Raginsky, of Montreal, Canada, will speak on the subject "Mental Suggestion as an Aid to Anesthesia"

## INCREASED PAY FOR MEDICAL OFFICERS

According to a recent announcement by Major General Raymond W Bliss, Surgeon General of the Army, all officers of the Regular Army Medical and Dental Corps, as well as all medical and dental officers serving voluntarily on extended active duty, will be paid an additional \$100 a month This addition to the incomes of such officers is regarded by the War Department "not as a pay increase but as an equalization measure designed to bring the incomes of Medical and Dental Corps officers more nearly in line with those of civilian doctors and dentists"

The additional compensation will be paid not only to officers who were on extended active duty as of September 1, 1947, the effective date of the act, but also to eligible officers of the Medical and Dental Corps who are commissioned in the Regular Army or Navy and who are volunteers for extended active duty within the limits of the act. The duration of these benefits is limited to the period of active service.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 9

## FRIDAY, OCTOBER 10

- \*9 00-10 00 a m Pulmonary Embolism Dr Lewis Dexter Joseph H Pratt Diagnostic Hospital  
\*10 00 a m-12 00 m Medical Staff Rounds Peter Bent Brigham Hospital  
12 00 m-1 00 p m Clinicopathological Conference (Boston Floating Hospital) Joseph H Pratt Diagnostic Hospital

## MONDAY, OCTOBER 13

- \*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital

## TUESDAY, OCTOBER 14

- \*12 15-1 15 p m Clinicopathological Conference Peter Bent Brigham Hospital  
8 00 p m Harvard Medical Society Amphitheater, Building D Harvard Medical School

## WEDNESDAY, OCTOBER 15

- \*9 00-10 00 a m Pediatric Clinicopathological Conference Dr James M Baty and H E MacMahon Joseph H Pratt Diagnostic Hospital  
\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital

\*Open to the medical profession

OCTOBER 6-10 American Public Health Association Page 456, issue of March 20

OCTOBER 6-17 New York Academy of Medicine Page 348, issue of August 28

OCTOBER 8 New England Dermatological Society Notice above.

OCTOBER 8-31 Joseph H Pratt Diagnostic Hospital Medical Conference Program Page 529

OCTOBER 9 Practical Points in Geriatrics Dr Roger I Lee Per tucket Association of Physicians 8 30 p m Haverhill

OCTOBER-DECEMBER Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital Page 348, issue of August 28

OCTOBER 13-18 Medicolegal Conference and Seminar for Pathologists Medical Examiners and Coroners Page 242, issue of August 14

OCTOBER 14 Harvard Medical Society Notice above

OCTOBER 29-31 New England Postgraduate Assembly Copley Plaza Hotel Boston

NOVEMBER 10 Joint Meeting of New England Society of Anesthesiologists and American Society of Anesthesiologists, Incorporated. Notice above

NOVEMBER 13-15 Association of Military Surgeons Annual Meeting Hotel Statler, Boston

FEBRUARY 6 American Board of Obstetrics and Gynecology Page 24, issue of August 14

APRIL 19-23 American College of Physicians Page xiii, issue of July 1

MAY 6-8 American Association for the Study of Goiter Part xiv, issue of July 31

MAY 11-15 American Association on Mental Deficiency Page 14, issue of July 24

## DISTRICT MEDICAL SOCIETIES

## MIDDLESEX EAST

- NOVEMBER 19  
JANUARY 21  
MARCH 24  
MAY 12 Annual meeting  
All meetings will be held at the Bear Hill Golf Club

## NORFOLK

- OCTOBER 28 Lahey Clinic Night  
NOVEMBER 25 Tufts Night  
JANUARY 27 Round-Table Discussion Bleeding from the Alimentary Tract  
FEBRUARY 24 Obstetric and Gynecologic Night  
MARCH 23 Harvard Night

## PLYMOUTH

- OCTOBER 16 Jordan Hospital, Plymouth  
NOVEMBER 20 Plymouth County Sanatorium, South Hanson  
JANUARY 15 Brockton Hospital, Brockton  
FEBRUARY 19 Toll House, Whitman  
MARCH 18 Goddard Hospital, Brockton  
APRIL 15 State Farm Bridgewater  
MAY 20 Lakeville Sanatorium, Lakeville

## 4 Censors' Meeting

- 8 Rutland State Hospital  
12 Grafton State Hospital  
10 Worcester City Hospital  
St. Vincent's Hospital  
Worcester State Hospital  
Memorial Hospital  
Hannan Hospital  
Meeting

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## STREPTOMYCIN THERAPY IN 52 CASES OF BACTERIAL INFECTION\*

LEWIS W. KANE, M.D.,† AND GEORGE E. FOLEY‡

BOSTON

**STREPTOMYCIN**, an antibiotic agent obtained from certain strains of *Actinomyces griseus*, was first described by Schatz, Bugie and Waksman<sup>1</sup> in 1944. Immediate interest was attracted to this agent because of its effectiveness in vitro against bacteria that had previously been resistant to the action of known antibiotic and chemotherapeutic agents. Animal studies have demonstrated that the toxicity of streptomycin is of a relatively low order,<sup>2</sup> and the results in the treatment of experimental infections have proved its effectiveness in vivo.<sup>3-5</sup> Clinical trials in the past two years have confirmed its low toxicity and demonstrated its value in the treatment of infections known to be resistant to the action of penicillin and the sulfonamides, such as those produced by gram-negative bacilli. Among the human infections known to respond to streptomycin treatment are tularemia,<sup>6-8</sup> meningitis due to *Haemophilus influenzae*,<sup>9</sup> and urinary-tract infections due to gram-negative bacilli.<sup>10</sup> The results of treatment of 1000 miscellaneous cases have recently been reviewed by the Committee on Chemotherapeutics of the National Research Council.<sup>11</sup>

It is the purpose of this paper to report in detail the results obtained in 52 cases treated with streptomycin. In this group are included urinary-tract infections, meningitis and epiglottitis due to *H. influenzae*, bronchiectasis, nonspecific urethritis and 1 case of septicemia caused by *Pseudomonas aeruginosa*.

### MATERIAL AND METHODS

All patients treated with streptomycin were hospitalized at the Massachusetts General Hospital or the Massachusetts Eye and Ear Infirmary.<sup>12</sup> They

were selected on the basis of the infecting organism after careful bacteriologic study. Most patients had previously been treated with penicillin or one of the sulfonamides and had failed to make a satisfactory clinical response. In most cases streptomycin was administered intramuscularly. Topical and aerosol streptomycin were used in certain cases in which they were considered to be of possible value.

Determinations of streptomycin sensitivity and body-fluid levels of the drug were carried out when indicated, according to the method described by Price, Nielsen and Welch.<sup>1</sup>

### URINARY-TRACT INFECTIONS

#### *Pyelonephritis and Cystitis*

Thirty-eight cases of pyelonephritis and 2 cases of cystitis were treated with streptomycin (Table 1). These cases were selected on the basis of infections due to gram-negative bacilli. In 32 cases the infecting organism belonged to the colon-aerogenes group. Of the remainder, 2 were due to *Ps. aeruginosa* and 2 to *Proteus vulgaris*, and 4 were mixed infections due to *Escherichia coli* in combination with *Ps. aeruginosa* in 3 cases and *Pr. vulgaris* in 2. No cases were treated in which indwelling catheters were being used. Cases with nonobstructing renal calculi or partial ureteral strictures were not excluded in this study, since it seemed important to determine the effect of streptomycin in the presence of these complications. Except when contraindicated, sulfonamides and less frequently mandelic acid and penicillin were employed in all cases prior to the initiation of streptomycin therapy.

A 0.1 per cent streptomycin solution in physiologic saline was given intramuscularly on a four-hour schedule, but the 2-a.m. dose was usually omitted because it was observed that effective urinary levels were maintained during the 10-p.m. to 6-a.m. interval. The total dosage varied from a minimum of 0.5 to a maximum of 2.0 gm a day. At first all cases were treated with 1 gm daily for ten days, but as more experience was gained, it was found that smaller doses (0.5 gm)

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[The streptomycin used in these studies was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Therapeutics and Other Agents.]

[This study was made possible by the close co-operation of the visiting and house staffs of the medical, surgical and pediatric services of the Massachusetts General Hospital and Massachusetts Eye and Ear Infirmary. We are indebted to Mrs. W. C. H. for aid in the technical work and the preparation of the manuscript.]

given for as little as three or four days were sufficient in cases in which the infecting organisms were extremely sensitive. In cases in which it was impossible to obtain the sensitivity of the infecting organism prior to the institution of therapy, 1 gm daily was used as an initial dose, and the response

three days and in 1 each within four and five days. The duration of therapy varied according to the rapidity with which the organisms disappeared from the urine. It soon became apparent that it was not necessary in most cases to continue treatment for more than three days after the urine first became

TABLE I *Results of Streptomycin Therapy in 40 Cases of Pyelonephritis and Cystitis*

CASE NO	AGE	DURATION OF DISEASE	RENAL COMPLICATIONS	ETIOLOGIC AGENT	INHIBITING LEVEL OF STREPTOMYCIN microgm / 100 cc	PREVIOUS THERAPY	STREPTOMYCIN DOSAGE	
							DAILY gm	TOTAL gm
1	42	1/12	—	<i>Esch coli</i>	—	Penicillin	1 0	12 6
2	26	22	Renal calculi, hydronephrosis and hydroureter	<i>Esch coli</i> <i>Pr vulgaris</i>	2500 1500	Penicillin and sulfonamide	1 0-2 0	19 9
3	36	1/12	—	<i>Esch coli</i>	—	Penicillin and sulfonamide	1 0	7 4
4	50	6/52	—	<i>Ps aeruginosa</i>	—	Penicillin and sulfonamide	1 0	7 6
5	33	16	Renal calculi	<i>Esch coli</i>	—	Sulfonamide	1 0	7 4
6	59	25/12	Hydroureter and stricture	<i>Esch coli</i>	—	Penicillin and sulfonamide	1 0	4 3
7	38	2/12	—	<i>Esch coli</i>	—	Sulfonamide	1 0	4 2
8	49	2/52	—	<i>Esch coli</i>	—	Penicillin and sulfonamide	0 9	5 7
9	5 5	1	Bilateral hydronephrosis and hydroureters	<i>Esch coli</i>	125	Penicillin and sulfonamide	0 5-1 0	5 7
10	38	6/365	—	<i>Esch coli</i>	—	None	0 9	3 9
11	59	11	—	<i>Esch coli</i>	—	Sulfonamide	1 0	5 4
12	38	6-7	—	<i>Esch coli</i>	—	Penicillin and sulfonamide	1 0	5 6
13	35	8/12	Renal calculi	<i>Esch coli</i>	—	Sulfonamide	1 2	10 0
14	58	14	Renal calculus	<i>Esch coli</i>	—	None	0 5	2 3
15	40	16	Hydronephrosis and hydroureters	<i>Esch coli</i>	2000	Sulfonamide	1 0	5 0
16	38	12	Hydroureters and dilated calyces	<i>Esch coli</i>	156	Sulfonamide	2 0	15 2
18	67	1/12	Renal calculi	<i>Pr vulgaris</i>	—	Sulfonamide	1 0	6 8
19	43	7	Bilateral renal calculi	<i>Esch coli</i> <i>Ps aeruginosa</i>	2000	Sulfonamide	1 0	7 6
20	58	1	—	<i>Esch coli</i>	—	Sulfonamide	1 0	8 0
21	62	12	—	<i>Esch coli</i>	—	Sulfonamide	1 0	6 6
22	32	5	Partial ureteral stricture	<i>Esch coli</i>	7 8	Penicillin and sulfonamide	1 0-2 0	10 0
23	22	2	Hypoplastic kidney	<i>Ps aeruginosa</i>	31 2	Penicillin	1 2-2 0	9 2
24	69	11/365	Incontinence	<i>Esch coli</i>	—	Sulfonamide	1 0	7 0
25	42	1/12	—	<i>Esch coli</i>	15 6	Sulfonamide	0 5	4 0
26	56	1/12	—	<i>Esch coli</i>	15 6	Penicillin and sulfonamide	1 0	4 4
27	69	4	Partial stricture of ureter	<i>Esch coli</i>	—	Penicillin and sulfonamide	1 0	6 4
28	2	15/365	—	<i>Ps aeruginosa</i>	125	Penicillin and sulfonamide	1 0	6 6
29	45	14/365	Cord bladder	<i>Esch coli</i>	62 5	Penicillin and sulfonamide	1 0-1 2	7 0
30	36	8/365	—	<i>Esch coli</i>	2000	Penicillin and sulfonamide	1 0	8 8
31	47	?	—	<i>Esch coli</i>	—	None	1 0	7 0
32	55	17	Slight hydronephrosis	<i>Esch coli</i>	15 6	Sulfonamide	0 5-1 0	7 0
33	36	1	—	<i>Esch coli</i>	—	Sulfonamide	0 5	3 8
34	24	4	Dilated calyces	<i>Esch coli</i>	—	Sulfonamide	1 0	6 8
35	6	4	Dilated calyces and pelvis	<i>Esch coli</i>	15 6	Penicillin and sulfonamide	1 0	7 6
36	40	15/365	—	<i>Esch coli</i>	1 5	Penicillin and sulfonamide	1 0	10 8
37	67	3/12	—	<i>Esch coli</i>	—	None	0 5-1 0	3 5
38	35	7	—	<i>Pr vulgaris</i>	—	Penicillin and sulfonamide	1 0	8 0
39	50	16/12	Atonic bladder	<i>Esch coli</i>	—	Sulfonamide	0 5	3 5
40	73	2	—	<i>Esch coli</i>	—	Sulfonamide	1 0	7 8
41	8	6/365	—	<i>Pr vulgaris</i> <i>Esch coli</i>	15 6	Sulfonamide	1 0-1 8	15 1

assayed by daily urine cultures. When this method was used, the dosage was raised if there was no response within three or four days. The reliability of this method is indicated by the fact that of the 30 cured patients followed by daily cultures while on streptomycin therapy, the urine in 17 (57 per cent) became sterile within one day, in 8 (26 per cent) within two days,\* in 3 (10 per cent) within

sterile. In no case was therapy continued for more than eleven days.

Whenever possible, the fluid intake was restricted to 2000 to 3000 cc daily. On the basis of the work done by Abraham and Duthie,<sup>13</sup> in which it was demonstrated that streptomycin is most effective in an alkaline medium, the urine was alkalinized in the majority of cases by means of sodium citrate. One teaspoonful of a 50 per cent solution was given orally three times daily. The reaction of each speci-

\*In 4 of these cases the urine was not cultured until the second day, and hence may actually have been sterile on the day following the institution of streptomycin therapy.

men was checked by nitrazine paper. In most cases this dosage was sufficient to maintain an alkaline urine, but occasionally the daily dosage had to be increased to five teaspoonfuls. In the occasional case with pulmonary or peripheral edema, potassium salts were substituted for sodium citrate.

collate when blood agar or Endo's medium failed to show growth.

All cases were classified as cured, improved or unimproved. Cases in which the original infecting organism disappeared under therapy and for a minimum of one week after all therapy had been dis-

TABLE 1 (Continued)

CASE NO.	RESULT	FIRST STERILE URINE CULTURE	FOLLOW UP CULTURES		REACTIONS	REMARKS
		days	NO.	PERIOD		
1	Cure	2	5	26		
2	No improvement		10	11	Fever Headache and vertigo	Resistant organisms
3	Cure	1	3	5	None	
4	Cure	1	10	106	None	
5	Cure	4	6	121	None	
6	Cure	1	5	122	None	
7	Cure	1	6	94	None	
8	Cure	1	5	58	None	
9	No improvement		1	1	None	
10	Cure	1	8	44	None	Sulfonamides contraindicated; <i>Str. faecalis</i> appeared after cessation of therapy. <i>Staph. albus</i> appeared after cessation of therapy.
11	Cure	1	0	57	None	
12	Cure	3	3	75	None	
13	Cure	1	11	100	None	Gamma streptococci appeared on 75th day.
14	Cure	1	3	5	None	
15	No improvement		4	26	None	Resistant organism
16	Cure	2	4	66	Skin eruption	
18	Cure	1	5	44	None	
19	No improvement		1	63	None	Resistant organism
20	Cure	1	6	47	None	
21	Cure	1	10	16	None	
22	Cure	2	4	37	None	Patient became reinfected with <i>Ps. aeruginosa</i> .
23	Cure	1	2	7	None	Patient pregnant during therapy.
24	Improvement		4	6	None	Patient catheterized every 8 hr. death from coronary disease.
25	Cure	3	3	20	None	
26	Cure	1	7	53	None	
27	Cure	1	3	37	None	
28	Cure	2	15	27	None	Inhibiting level increased to 500 microgm. during therapy.
29	Improvement		7	16	None	Patient catheterized every 4 to 6 hr. and became infected with resistant <i>Ps. aeruginosa</i> (2000 microgm.) while on therapy.
30	No improvement		1	1	None	Sulfonamides contraindicated. blood dyscrasia. Resistant organism.
31	Cure	2	12	58	None	Chronic pyelonephritis relapse after 56 days.
32	Cure	2	2	13	None	
33	Cure	2	3	10	None	
34	Improvement	3	1	41	None	Relapse on cessation of drug; no increase in resistance of organism.
35	No improvement		22	59	None	Death from pulmonary embolism.
36	Cure	5	5	8	Local pain	Gamma streptococci appeared 9 days after cessation of therapy.
37	Cure		4	20	None	
38	Cure	1	8	28	Local pain	
39	Cure	2	4	69	None	Cystitis.
40	Cure	1	4	45	None	Cystitis.
41	Improvement	2	2	23	None	Inhibiting level increased to 2000 microgm. during therapy.

Clean voided urine specimens were obtained daily on male and catheterized specimens on female patients. At the beginning of this study all urine sediments were cultured in sodium thioglycollate in addition to the usual blood agar and Endo's medium. Sodium thioglycollate was chosen, since it has been shown experimentally that this substance, as well as glucose, reduces streptomycin activity.<sup>14</sup> This was soon discontinued, however, since in no case was a positive culture obtained in sodium thiogly-

collate when blood agar or Endo's medium failed to show growth. It was believed that if the urine remained sterile for one week the infection would not relapse, since in the 30 cases considered cured on this basis, there was only one questionable relapse. This case, in which the urine again became positive for *Esch. coli* fifty-six days after therapy had been discontinued, may have represented reinfection rather than an actual relapse. The majority of cases were followed for periods longer than one week (Table 1). No case

was considered cured unless a minimum of two follow-up cultures were done. In most cases, more than two cultures and in some as many as fifteen were obtained over a period of several months. Cases were classified as improved when urine cultures did not become completely sterile, but in which there was a marked reduction in the colony count, as well as improvement in the urinary sediment. Cases were considered unimproved when there was neither clinical nor bacteriologic response to therapy.

The results of streptomycin therapy in 40 cases of urinary-tract infections when classified according to the criteria mentioned above were 75 per cent

respond, whereas another (Case 14) responded to streptomycin after having been infected for fourteen years.

In the improved group of 4 cases, the urine could not be completely sterilized in 2 (Cases 24 and 29), possibly because of the necessity of performing catheterizations every four to eight hours. An additional patient (Case 34) might have been cured had therapy been more intensive and prolonged. In only 1 patient (Case 41) could failure to sterilize the urine be attributed to the acquisition of streptomycin resistance by the infecting organism.

Of the 6 cases classified as unimproved, 3 (Cases 2, 15 and 19) were infected with streptomycin-

TABLE 2 Results of Streptomycin Therapy in Cases with and Those without Urinary-Tract Damage\*

TYPE OF CASE	TYPE OF ORGANISM	NO OF CASES	PATIENTS CURED		PATIENTS IMPROVED		PATIENTS UNIMPROVED		TOTAL PERCENTAGE CURED OR IMPROVED
			NO	PERCENTAGE	NO	PERCENTAGE	NO	PERCENTAGE	
No urinary-tract damage	Susceptible	21	19	91	2	9	0	—	100
Urinary-tract damage	Susceptible	15	11	74	2	13	2	13	87
Totals		36	30		4		2		
Averages				83		11		6	95
No urinary-tract damage	Resistant	0	0	—	0	—	0	—	—
Urinary-tract damage	Resistant	4	0	—	0	—	4	100	—

\*One patient was probably inadequately treated. Another improved markedly prior to the acquisition of resistance, despite the persistent bacteriuria that continued after the acquisition of resistance; the improvement was maintained during the follow-up period.

cured, 10 per cent improved and 15 per cent with no response. Thus, 85 per cent of all cases were definitely aided by streptomycin therapy. These figures indicate that good results may be expected in the majority of urinary-tract infections due to gram-negative bacilli, despite the fact that they have failed to respond to other antibiotic and chemotherapeutic agents. In this study the best results were obtained in cases with no structural damage to the urinary tract in which the infecting organism was sensitive to streptomycin. In this group of 21 cases 91 per cent were cured and 9 per cent improved (Table 2), there were no failures.

Moderate structural damage, such as dilated calyces, slight hydronephrosis, partial stricture of a ureter or small nonobstructing renal calculi, did not seem to preclude a cure if the infecting organism was sensitive (Cases 5, 6, 13, 14, 16, 18, 22, 23, 27, 32 and 39).

Infections with organisms found to have resistance in vitro that was higher than the levels obtained in the urine were unimproved by streptomycin therapy (Cases 2, 15, 19 and 30). One patient (Case 41) in whom resistance was acquired during therapy had shown marked clinical and bacteriologic improvement prior to the development of resistance.

The duration of infection seemed to be of importance only in that it led to marked structural changes and the formation of obstructive renal calculi. One patient (Case 30) in whom the duration of the infection was only eight days, failed to

respond, and in addition there were structural changes in the urinary tract, such as dilatation of the calyces or ureters. Two of these patients (Cases 2 and 19), in addition to harboring resistant organisms and having structural damage, had renal calculi. Only 1 patient with no structural complications (Case 30) failed to respond. This patient was infected with an extremely resistant organism. Failures resulted in 2 patients (Cases 9 and 35) who had streptomycin-sensitive organisms and extensive renal damage as a result of longstanding infection.

Two cases were considered to have relapsed. One of these patients (Case 35) relapsed as soon as streptomycin was discontinued, undoubtedly because of extensive renal damage. In the other (Case 31), relapse after fifty-six days may actually have represented a reinfection.

It is of interest that 1 patient (Case 29) became reinfected with another organism while on streptomycin therapy, but this case required repeated catheterizations, and the reinfected organism was a streptomycin-resistant *Ps aeruginosa*. An additional patient (Case 22), with a partial stricture of the right ureter, was cured of an *Esch coli* infection, but thirty-seven days later became reinfected with *Ps aeruginosa*.

Case 41 deserves special comment. The patient was an eight-year-old child who came into the hospital in a comatose, moribund condition due to a fulminating *Esch coli* pyelonephritis. The nonpro-

tein nitrogen was 165 mg per 100 cc and the blood carbon dioxide 17.2 milliequiv per liter. Because of the marked impairment in renal function sulfonamides were contraindicated, and streptomycin was begun immediately on entry. The urine culture became negative within forty-eight hours, and the renal function began to improve. There is no doubt that streptomycin, in conjunction with fluid and salt replacement, was responsible for saving this child's life.

### Nonspecific Urethritis

It appears that at least a portion of cases of urethritis that have previously been considered to be nonspecific, in the sense that they are nongonorrheal and nonpyogenic in origin, are due to infection by organisms belonging to the pleuropneumonia group.<sup>18</sup> On the basis that these organisms are small, gram-negative bacillary forms, it

therapy, there was less dysuria and urgency, the red and white cells in the urinary sediment were markedly reduced, and pleuropneumonia-like organisms could no longer be cultured from the urine. On discharge from the hospital the patient was entirely asymptomatic and remained so during a follow-up period of six months. This infection was of three years' duration, and during that time the patient had never been symptom-free for more than a few days.

The patient in Case 1 received 2.0 gm of streptomycin intramuscularly daily for ten consecutive days. Improvement in urinary symptoms was noted forty-eight hours after the institution of therapy, simultaneously with a marked reduction in the number of red and white cells in the urinary sediment. Pleuropneumonia-like organisms could not be cultured from the urine after the institution of strepto-

TABLE 3 Results of Streptomycin Therapy in Nonspecific Urethritis Apparently Due to Pleuropneumonia-like Organisms

CASE NO	AGE	DURATION OF DISEASE	PREVIOUS THERAPY	STREPTOMYCIN	DOSAGE	RESULT
	yr			DAILY	TOTAL	
				gm	gm.	
1	49	2 mo.	None	2 0	19 2	Cure
2	14	16 yr	Pe icillin and sulfo amide	4 0	26 4	Failure
3	26	3 yr	None	1 0-2 0	13 2	Cure

seemed worth while to try streptomycin therapy, although the sensitivity of the organisms in vitro had not been established because of technical difficulties.

Three cases of infection apparently due to pleuropneumonia-like organisms\* were treated with streptomycin (Table 3). One of these cases was a simple urethritis (Case 1), 1 a urethritis associated with prostatitis (Case 2) and 1 a urethritis with hemorrhagic cystitis (Case 3). In all these cases no other micro-organisms could be isolated consistently from the urine. On the other hand, in Case 3 pleuropneumonia-like organisms were isolated from four urine samples, and in Case 2 in five instances from prostatic secretions or urethral discharges prior to the institution of streptomycin therapy. In Case 1 the fact that only one positive culture could be obtained despite repeated attempts is understandable in view of the difficulty associated with the isolation and cultivation of these organisms.

The urine was rendered alkaline in all cases. In Case 3 a total of 2.0 gm of streptomycin was given intramuscularly daily (0.4 gm every four hours, the 2-a.m. dose being omitted). Because of the improvement on the sixth day, the dose of streptomycin was reduced to 1.0 gm daily, and continued for five additional days. Three days after the institution of

mycin therapy symptoms did not reappear during a follow-up period of four months.

In Case 2, a total of 4.0 gm of streptomycin intramuscularly was given daily for eight consecutive days. On the day following the institution of therapy, the urethral discharge disappeared. Pleuropneumonia-like organisms, however, were consistently cultured from prostatic secretions and urine samples during therapy. The urethral discharge reappeared when streptomycin was discontinued.

### Haemophilus Influenzae INFECTIONS

Four cases of Type B *H. influenzae* infection were treated with streptomycin (Table 4). Two of these were meningitis, and 2 were epiglottitis. In addition to streptomycin the patients with meningitis received sulfadiazine. One patient also received 300 mg of Type B *H. influenzae* antiserum. A Quellung reaction was not obtained, however, with this patient's serum, and it is doubtful whether the antiserum influenced the course of the disease.

Both patients with meningitis received 0.05 to 0.1 gm of streptomycin intrathecally each day, as well as 0.6 to 0.8 gm intramuscularly, divided into six daily doses given every four hours. The spinal fluid in both cases became negative for *H. influenzae* within forty-eight hours after streptomycin therapy had been instituted. Although a bacteriologic cure

\*We are indebted to Dr. L. Difene of the Department of Pathology and Bacteriology, Massachusetts General Hospital, for the isolation and identification of these organisms.



was effected relatively early, clinical response was slower in appearing

Two cases of *H influenzae* epiglottitis requiring tracheotomy were treated with streptomycin. Each patient received 0.2 gm every four hours intramuscularly. In both cases colonies of Type B *H influenzae* were recovered from the pharynx as well as the blood. The patient in Case 3 received penicil-

were bronchiectasis, 1 a lung abscess, and 1 a case of *Ps aeruginosa* septicemia

The 3 patients with bronchiectasis were treated with streptomycin aerosol. These cases had been treated previously with penicillin aerosol with only slight improvement in the clinical condition. Because they continued to raise large volumes of sputum from which *Esch coli* grew abundantly,

TABLE 4 Results of Streptomycin Therapy in *H influenzae* Infections

CASE No	DIAGNOSIS	AGE	DURATION OF DISEASE	PREVIOUS THERAPY	STREPTOMYCIN DOSAGE		CONCURRENT THERAPY	RESULT	FIRST STERILE CULTURE	REACTIONS	REMARKS
					DAILY gm	TOTAL gm					
1	Meningitis	15 mo	120 hr	Penicillin and sulfonamide	0.8*	5.9	Sulfadiazine	Cure	1	None	—
2	Meningitis	9 mo	44	Penicillin and sulfonamide	0.05-0.1†	0.35	Sulfadiazine 300 mg of antiserum	Cure	2	Skin eruption	Blood culture positive for <i>H. influenzae</i> . Quellung reaction never obtained on blood serum.
3	Epiglottitis	11 yr	48	Penicillin and sulfonamide	1.2	7.8	Tracheotomy and penicillin	Cure	2	Skin eruption	Infection extended into anterior and lateral aspects of neck.
4	Epiglottitis and tracheo-bronchitis	3 yr	15	None	1.2	10.6	Tracheotomy and penicillin	Cure	4	Skin eruption	Blood culture positive for <i>H. influenzae</i> .

\*Intramuscular route.

†Intrathecal route.

lin and sulfadiazine for two days before streptomycin therapy. Because the temperature remained high, the throat culture remained positive for *H influenzae* and there seemed to be a spread of the pharyngeal infection, streptomycin therapy was started. On the following day the temperature dropped from 104 to 100°F, and *H influenzae* disappeared from the throat culture forty-eight hours after the institution of therapy. In Case 4 strepto-

aerosol streptomycin was believed to be indicated. Doses of 2 cc containing 50,000 units each of combined streptomycin and penicillin were inhaled every three or four hours. When combined therapy was employed the sputum was rendered sterile except for yeasts and fungi. Only 1 of the patients so treated was considered to have been benefited. Although no conclusion can be drawn from such a small number of cases, it appears that combined

TABLE 5 Results of Streptomycin Therapy in Miscellaneous Infections

CASE No	DIAGNOSIS	AGE	DURATION OF DISEASE	ETIOLOGIC AGENT	SOURCE OF CULTURE	PREVIOUS THERAPY	STREPTOMYCIN		RESULT
							DAILY	TOTAL	
							gm	gm	
1	Bronchiectasis	57	14 yr	<i>Esch coli</i>	Sputum	Penicillin* and sulfonamide	0 1†	0 7	No improvement
2	Bronchiectasis	50	9 yr	<i>Esch coli</i>	Sputum	Penicillin*	0 28†	1 44	Improvement
3	Bronchiectasis	79	1 yr	<i>Esch coli</i>	Sputum	Penicillin*	0 2-0 24*	1 0	No improvement
4	Lung abscess	42	13 days	<i>H influenzae</i>	Sputum	Penicillin* and sulfonamide	0 25	4 05	Improvement
5	Septicemia	1	21 days	<i>Ps aeruginosa</i>	Blood, nasal washings, urine, stool and scalp abscess	Penicillin and sulfonamide	0 6-1 2	17 2	Cure
							0 6†	5 0	

\*Given as aerosol.

†Given as aerosol combined with penicillin in same nebulizer.

‡Given orally.

mycin was started immediately on entry. Although much more severely ill on admission than the patient in Case 3, this patient had a much smoother convalescence and a shorter period of hospitalization.

#### MISCELLANEOUS INFECTIONS

Five cases classified as "miscellaneous" were treated with streptomycin (Table 5). Three of these

streptomycin and penicillin aerosol should be given further trial in cases of bronchiectasis.

A case of lung abscess, thought to be due to *H influenzae*, since this organism was obtained in pure culture from the sputum, was treated with combined penicillin and streptomycin aerosol. The sputum was rendered sterile, and in twelve days there was marked improvement in the clinical con-

lition and the abscess cavity was considerably reduced in size.

One case of *Ps. aeruginosa* septicemia (Case 5) seems worthy of comment, since in view of the high mortality resulting from such infection, streptomycin is considered responsible for the recovery. (The patient was an eleven-month-old child who had had diarrhea for two weeks and had been treated with penicillin and sulfasuxidine at another hospital. On admission to the Pediatric Service of the Massachusetts General Hospital the temperature was  $106^{\circ}\text{F}$ . *Ps. aeruginosa* was cultured from the blood, urine, stool and nasal washings. The patient was given 0.6 gm. of streptomycin daily, which gave a blood level of 16.0 microgm. per cubic centimeter. When the resistance of the infecting organism was found to be 16 microgm., the daily dose was increased to 1.2 gm. This dosage gave a blood level of 65 microgm. per cubic centimeter. The blood culture became negative on the third day of therapy, and the patient continued to improve. Several days later she developed a scalp abscess from which *Ps. aeruginosa* was recovered. In addition to intramuscular streptomycin she received 0.6 gm. of oral streptomycin daily, since she continued to carry an abundance of *Ps. aeruginosa* in the stools. After the institution of oral therapy, *Ps. aeruginosa* as well as *Esch. coli* gradually disappeared from the stool.

### DISCUSSION

#### Urinary-Tract Infections

Only a few publications have appeared describing the results of the streptomycin treatment of urinary-tract infections due to gram-negative bacilli. Herrell and Nichols<sup>6</sup> recorded good results in 10 of 13 cases, whereas Keefer et al.<sup>11</sup> reported recoveries in 42 per cent and improvement in 35 per cent of 409 cases. Less favorable results were obtained by Finland and his associates,<sup>16</sup> who observed failures in 8 of 12 treated cases, and Nichols and Herrell,<sup>17</sup> who reported good results in only 42 per cent of cases.

Of the 40 cases of urinary-tract infections reported in this paper, cures were obtained in 75 per cent and improvement in 10 per cent. Since these figures are somewhat higher than those reported in other publications, it seems worth while to compare the method of therapy employed with those used elsewhere. On the basis of the studies of Abraham and Duthe,<sup>18</sup> in which it was shown that there is a tenfold increase in streptomycin activity when the reaction of the urine is raised from pH 6.0 to 7.5, it seemed desirable to alkalinize the urine in all cases during therapy. In the 12 cases reported by Finland et al.<sup>16</sup> no attempt was made—with a single exception—to render the urine alkaline. Since no mention is made of this in the reports of Herrell and Nichols<sup>6</sup> and Keefer and his co-workers,<sup>11</sup> such an effort was presumably not made. Because the route of administration of streptomycin, the daily dose and the duration of therapy were essentially

the same in this study as those reported elsewhere, the higher percentage of good results is considered to be due to the fact that the urine was rendered alkaline in each case.\*

Failure of streptomycin therapy in many cases has been attributed to the rapid development of resistance by the infecting organism. Finland et al.<sup>16</sup> showed that in 8 of 10 cases of urinary-tract infection the rapid acquisition of resistance was responsible for the failure of therapy. It is of great interest that in only 1 case of the 40 reported in this study did resistance develop. The only important difference between the method of therapy employed and those reported elsewhere was the insistence on an alkaline urine in each case during treatment. Accordingly, it seems highly likely that alkalinization is responsible for the failure of the organisms to develop resistance and, as a consequence, for the more favorable results obtained in this study. The mechanism for the failure to develop resistance in an alkaline medium is obscure. It cannot be entirely explained by the greater activity of streptomycin in an alkaline substrate, since in the cases in which the infecting organisms were not completely eliminated no increase in resistance could be demonstrated.

The results of the treatment of urinary-tract infections with streptomycin indicated that urinary levels above the minimal inhibiting dose of the infecting organism must be obtained if success is to be expected. If the minimal inhibiting dose of the organism is higher than the level that can be obtained in the urine, a resistant organism may be said to be present and failure will ensue. The presence of a susceptible organism does not necessarily indicate that a cure will result if marked structural damage is present, but minor and even moderate changes do not necessarily preclude a cure.

In this study it was decided to treat all cases regardless of the initial sensitivity of the organism to determine the relation between action *in vitro* and clinical response to the drug. Of the 40 unselected cases treated with a daily dose varying between 0.5 and 2.0 gm., 75 per cent were cured and 10 per cent were improved. On this basis it is believed that 2.0 gm. of streptomycin daily should produce satisfactory results in the majority of cases. Although the determination of organism sensitivity is desirable before institution of therapy, it is not essential. Since the urine became sterile in 83 per cent of cases forty-eight hours after the institution of therapy, if no clinical response is observed within that time, the sensitivity of the organism should be determined and the dose increased accordingly.

The variations in streptomycin sensitivity among strains of the same organism are well illustrated in

\*Since the completion of this paper for publication an article on the favorable influence of alkali in streptomycin therapy of urinary-tract infections by Harris et al.<sup>19</sup> has appeared. In their series of 14 cases 8 were cured. These investigators have noted that the maintenance of an alkaline urine during streptomycin therapy seemed to prevent the infecting organism from acquiring resistance.

this series. For example, the sensitivity of different strains of *Esch coli* varied from 1.5 microgm (1.5 units) to more than 2.0 mg (2000 units) per cubic centimeter. Other strains of *Esch coli* that were inhibited by as little as 0.5 microgm (0.5 unit) per cubic centimeter have been encountered in this laboratory. In general, the majority of strains of *Esch coli* isolated were sensitive to concentrations of streptomycin that are easily obtainable in the urine, the resistant strains being the exception among this species. Three of the 4 resistant cases (Table 1) were infected with *Esch coli*, whereas another was infected with both *Esch coli* and *Pr vulgaris*. These cases represent only about 10 per cent of all cases from which *Esch coli* was isolated either alone or in combination with other organisms.

It seems to be the consensus that of the gram-negative bacilli, *Ps aeruginosa* is the most uniformly resistant to streptomycin. Two of the four strains of this species, however, encountered in urinary-tract infections were found to be susceptible to fairly small amounts of streptomycin in vitro. These patients were cured of their infections. An additional case was cured, but unfortunately the organism could not be studied for sensitivity in vitro. In view of the clinical response, however, this strain was undoubtedly moderately sensitive, since a rather low daily dose of streptomycin was used. In only 1 of the 4 cases of urinary-tract infection due to *Ps aeruginosa* was resistance in vitro encountered. This case did not respond to therapy. With the exception of Case 2 (Table 1), the strains of *Pr vulgaris* studied were uniformly susceptible to streptomycin.

Because of the marked individual variations among strains of the same bacterial species, the clinical result cannot be predicted solely on the basis of species identification. For example, the infecting organism may be a resistant strain of *Esch coli*, which as a species is considered to be susceptible to streptomycin. Likewise, a given infection may be due to a susceptible strain of *Ps aeruginosa*, which as a species is generally considered to be moderately resistant to streptomycin. Bacteriologic response or sensitivity in vitro should be used as a guide to therapy, the former is perhaps preferable to the latter, since sensitivities in vitro and in vivo are not always parallel.

It might be noted that in mixed infections of Lancefield Group D streptococci (*Str faecalis*) or *Staph albus* and gram-negative bacilli, although streptomycin cleared the urine of the latter organisms, it failed to have any effect on the gram-positive organisms. It is also of interest that in 4 cases *Str faecalis* or *Staph albus* appeared in the urine after therapy was stopped. The majority of Lancefield Group D streptococci studied in vitro were resistant to the streptomycin levels obtained with the dosages used in this study.

### Nonspecific Urethritis

Dienes and Smith<sup>19</sup> were able to isolate pleuropneumonia-like organisms from 4 cases of nonspecific chronic prostatitis. More recently, Beveridge et al,<sup>20</sup> in Australia, were able to isolate these organisms in 20 per cent of 70 cases of nonspecific urethritis. These workers were unable to find this organism in the normal male urethra. It seems reasonable to assume that pleuropneumonia-like organisms may under certain conditions be responsible for nonspecific urethritis, prostatitis and cystitis.

Because pleuropneumonia-like organisms are small, gram-negative bacillary forms, it seemed worth while to determine the therapeutic effect of streptomycin on cases of nonspecific urethritis and prostatitis from which these organisms could be recovered. In 2 cases, within seventy-two hours of the institution of streptomycin therapy there was a marked decrease in the urethral discharge, as well as a decrease in the number of red and white cells in the urinary sediment. Pleuropneumonia-like organisms could not be recovered after the institution of streptomycin therapy. These patients remained symptom-free for the duration of follow-up periods of four and six months. The third patient appeared to improve while on therapy, but pleuropneumonia-like organisms never disappeared and a relapse occurred when therapy was discontinued. The disappearance of the organisms in 2 cases simultaneously with the onset of clinical improvement seems to support the bacteriologic evidence that pleuropneumonia-like organisms are responsible for certain cases of nonspecific urethritis, prostatitis and cystitis. Since the pleuropneumonia-like organisms probably do not constitute a homogenous group, the success or failure of streptomycin therapy depends in part on the susceptibility of the infecting organism. The failure of Case 2 to respond may have been due to the fact that the patient was infected with a resistant strain.

### H Influenzae Infections

Two patients with Type B *H influenzae* meningitis treated with streptomycin recovered. In addition to streptomycin, both received sulfadiazine. One patient also received two doses of specific antiserum. Since a *Quellung* reaction was not obtained with serum from this case, it is doubtful whether the antiserum contributed to the recovery. In both cases the organisms disappeared from the spinal fluid after forty-eight hours of therapy.

The good results obtained in these 2 cases are similar to those reported by others in which antiserum was not used.<sup>10, 11, 21</sup> A recent report by Alexander et al,<sup>22</sup> however, indicates that the severer cases of *H influenzae* meningitis may require specific antiserum in addition to streptomycin and sulfadiazine.

Two cases of *H. influenzae* epiglottitis requiring immediate tracheotomy were treated with streptomycin. In addition, 1 patient received penicillin and sulfadiazine for two days before the institution of streptomycin therapy. Streptomycin was given in this case because throat cultures remained positive for *H. influenzae* and because there seemed to be a spread of pharyngeal infection. Forty-eight hours after streptomycin therapy had been started, the temperature had dropped considerably and *H. influenzae* disappeared from the throat. The other case, in which streptomycin therapy was started immediately on admission, had a much smoother and a shorter convalescence. These results indicate that streptomycin is a valuable adjunct to the treatment of *H. influenzae* epiglottitis.

### Miscellaneous Infections

Three cases of bronchiectasis, whose sputums contained gram-negative bacilli predominately, were treated with streptomycin aerosol. All patients had previously been treated with penicillin aerosol with only slight clinical improvement prior to therapy with combined streptomycin and penicillin aerosol. In 2 cases *Esch. coli* disappeared from the sputum within four days of the institution of combined therapy. It is of interest that repeated sputum cultures failed to grow anything other than a few colonies of *Monilia* during and for some time after combined aerosol therapy. In both cases the sputum was reduced somewhat in volume, but in only 1 was there a simultaneous improvement in the clinical condition. In the third case, although there was a reduction in the number of colonies of *Esch. coli*, there was no diminution in the volume of sputum, nor was there any improvement in the patient's condition. These results indicate that although the sputum may be rendered sterile, clinical improvement may not ensue. This raises a question regarding the significance of the presence of *Esch. coli* in the sputum in bronchiectasis. In certain cases the organism is undoubtedly responsible for a low-grade infection, whereas in others it may simply be a commensal saprophyte. In the former case streptomycin therapy may prove to be of definite value, whereas in the latter, although *Esch. coli* can be eliminated from the sputum, clinical improvement may not follow.

One case of postoperative lung abscess believed to be due to *H. influenzae* was treated with combined streptomycin-penicillin aerosol. Previous to the addition of streptomycin, penicillin aerosol alone was used without improvement in the patient's course. After the institution of combined therapy, *H. influenzae* disappeared promptly, and there was a simultaneous reduction in the volume of sputum. The patient improved, and the abscess cavity was reduced in size. This case is still under observation.

### Reactions

Eight of the 52 patients treated (15 per cent) experienced reactions that were considered to be due to streptomycin. These were relatively unimportant, and in most cases therapy was continued despite these manifestations. One patient complained of headache and vertigo, and 2 of pain at the injection site. Another developed a febrile reaction, and skin eruptions were observed in 4. The latter took the appearance of a papular, erythematous eruption that was somewhat pruritic. Three of the 4 patients who developed skin manifestations were children who, because of their small size, received a relatively larger dose than the adults.

### SUMMARY

Thirty-eight cases of pyelonephritis and 2 of cystitis due to gram-negative bacilli were treated with streptomycin. Cure was effected in 75 per cent, and improvement in 10 per cent, and 15 per cent failed to respond. Despite moderate renal damage and the presence of small nonobstructing renal calculi, cure resulted if the infection was due to a susceptible organism.

Patients infected with organisms with resistance in vitro greater than the levels that could be obtained in the urine with the dosage used in this study failed to respond. The acquisition of resistance by the infecting organism was not responsible for the failures reported. An appreciable increase in resistance was observed in only 1 case.

Two of 3 cases of nonspecific urethritis in which only pleuropneumonia-like organisms were isolated responded clinically and bacteriologically to streptomycin therapy.

Two cases of *Haemophilus influenzae* meningitis responded well to streptomycin therapy.

Recovery in 2 cases of *H. influenzae* epiglottitis seemed to be hastened by streptomycin therapy.

The favorable outcome in 1 case of *Pseudomonas aeruginosa* septicemia was undoubtedly due to the prompt use of streptomycin.

Of 3 cases of bronchiectasis in which *Escherichia coli* was the predominating organism in the sputum, only 1 showed clinical improvement as a result of treatment with combined penicillin and streptomycin aerosol.

One patient with lung abscess thought to be due to *H. influenzae* seemed to improve on combined penicillin and streptomycin aerosol.

Minor toxic reactions were observed in 15 per cent of cases.

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## MEDICAL MOTION PICTURES IN PRIVATE PRACTICE\*

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PRIVATE practice, especially in rural communities, often makes an active physician believe that he is no longer practicing scientific medicine. He must fight the impression that the distance between him and the nearest medical center is directly responsible for the distance he seems to be from ever producing anything of value to medical science. When faced with the reality of a patient at home, he is sure to remember the skillful correlation of x-ray, laboratory and clinical facts that gave him such pride as an intern and to feel dismayed at the seeming hypocrisy of entering a private home to undertake treatment with no support beyond his own unaided judgment. Sooner or later, however, he will meet a new situation that would not have been possible in his beloved hospital, and some makeshift surgery or substitute drug will produce surprising results. With this will come the realization that his everyday work is actually a series of medical studies, and the success of his extemporizing will give him the comforting assurance that he has used originality equal to any that his former classmates could have shown in their research laboratories. This realization will bring a desire to share the observation with other

physicians. The private practitioner will then need a medium of expression that has not been rigidly standardized but has concrete value as a presentation of the patient, even though it is technically incomplete because of its lack of bibliography, tabulated data and controlled experimentation. Amateur motion pictures will provide him with such a medium, and it is the purpose of this discussion to present evidence that the technics of motion-picture photography on medical subjects are well within the scope of a private practice.

Everyone has enjoyed motion pictures made by the popular producers in Hollywood. All of us are somewhat acquainted with the lusty offshoot doing profitable service in business advertising. Every physician has seen some of the films prepared in the large hospitals and clinics and having to do with operative surgery, medical education or public health. None of us have become sufficiently acquainted in a medical way with the humble amateur following his hobby in his own narrow circle but fully capable of producing pictures of professional clearness. Many a physician has been portraying the affairs of his own family but, with equipment right at his elbow, has never turned his hobby toward his medical work to discover how much it can enliven his practice with pictorial records of unusual cases. With the aid of motion pictures, a case history becomes an epic for demonstration at a medical meeting. To produce these films, the private practitioner needs information and gentle persuasion to convince him that motion pictures can be taken of his medical curiosities with equipment that does not require a studio and does not concern itself with darkrooms and film processing,

\*An inquiry among active members of the New Hampshire Medical Society early in 1947 disclosed the following figures from the first two hundred replies: owners of motion-picture cameras 65 (32.5 per cent), with 16 who had taken films of patients and 8 who had asked others to take pictures; physicians who did not own motion-picture cameras numbered 135 (62.5 per cent); those who had taken pictures with cameras belonging to others, 20; and those who had asked others to take pictures, 13. Potential motion-picture makers thus numbered 98, or 49 per cent of physicians who made replies.

Relatively few of the physicians in this "interested group" are specialists or are associated with clinics having photographic departments. It therefore seems that clinical motion-picture records in private practice should be emphasized as a practical development of this interest.

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except in the remote headquarters to which he mails the film carton

### SUBJECT MATTER

The physician who wishes to record his experiences must not forget to make his sequence of pictures logical and systematic so that the interest of his audience will not be lost. Certain limitations in the choice of subject matter can wisely be observed. Subjective symptoms will give no pictorial impression, and the sickest patient will look at ease on the screen unless he is evidencing his inward discomfort by attitude, gesture or grimace. Records of most of the abdominal emergencies will be limited to pictures of the actual surgical procedures. Growths and external anomalies will lend themselves well to views before and after treatment. Fractures will have no pictorial significance unless there is obvious deformity or a well explained series of x-ray studies, although the technic of reduction and the apparatus for fixation will be excellent for the film record. Many of the limitations can be overcome by diagrams and charts, which are incorporated in the finished series of otherwise disjointed pictures.

Motion is the essence of this type of pictorial recording. It is almost too obvious to note that the presence of motion is the factor that gives medical motion pictures superiority over still pictures when the restoration of a function or an alteration of gait is a vital sign of clinical progress. If wanted, still pictures can be made by the thousand from the motion-picture film by the simple process of enlargement of single frames.

The private practitioner may carry out his medical filming along several lines, which may merge at many points. He may begin by taking pictures of all sorts of interesting cases and putting them all in a "medical scrapbook." Such views taken at random will often include different stages of progress in the same patient, and these can be removed from the collection to be spliced together with a few diagrams and explanatory titles to make a complete case record. A little planning in a case that promises interesting developments will usually result in a better medical thesis because it will be possible to arrange visual emphasis by comparisons with a normal and by the inclusion of extra pictorial data on tests that might not actually be required by the treatment. The medical motion-picture maker must be guided by foresight into the reactions of his future medical audience, and he must be bound by a self-imposed law that the material has to be of clinical importance and has to be presented in a colorful but still accurate manner.

Even though the private practitioner may not include in his daily work any actual surgery, he will occasionally be interested in following a case through the operating room. He will probably do this repeatedly in the same hospital and from

experience learn the specific lighting conditions and the facilities for picture taking. Surgery offers the most spectacular but also the most exacting field for the amateur movie maker. Since the type of disease involved determines whether or not the procedure is suitable for pictures, the photographer must have the co-operation of the surgeon and must be ready to abandon his plans when there is deep dissection within the abdomen or in any similar cavity. Motion pictures under these conditions are beyond the reach of the usual amateur, and the procedures can be much better demonstrated by diagrams. Among the most favorable surgical subjects for motion-picture photography in the operating room are amputations, excisions of large tumors, plastic operations and others with similar obvious surface details. No better scenario was ever written than a cesarean section.

### TECHNIC

No one can talk about taking pictures of any kind without dwelling on the subject of exposure. For the motion-picture maker this detail has been reduced to a single step completed by setting of the size of the opening in front of the lens. The other camera factors remain standard because of their fixed relation to the speed of the action and of future projection. On most cameras there is a dial for setting the diaphragm according to the amount of light falling on the subject under conditions described in words that have been etched on a plate or printed card attached near the lens mount. The photographer must judge the suitable point according to these descriptions and set the aperture at the corresponding figure. The same figures are used in the directions that come with the film and with such accessories as photo-flood lighting units and title holders. With certain types of lighting and in definite places the motion-picture maker will discover that with his camera no satisfactory picture can be taken without artificial lighting or by moving of the subject into a better light. He will do well to learn early that an improperly exposed strip of film spliced into the finished film will spoil the effectiveness of otherwise excellent exposures.

Absolute rock-like steadiness of the camera while pictures are being taken is essential. Rapid swinging of the camera and even the small undulations caused by excited breathing will produce a giddiness that is distressing. Swinging of the camera during the taking of pictures is permissible only when there is a steady following of a moving object that itself retains a relatively fixed position in the frame of the picture or when slowly "tilting" or "panoraming" toward the center of interest across features of the scene that have such important bearing that they cannot be shown effectively in separate views. Thus, a close view of a patient with extensive edema can be obtained by moving slowly from the swollen feet to the region

of the face. A tripod is the standard means of securing steadiness for the camera. Other commercially made gadgets are available, but even without these assistants it should be possible for the photographer to hold the camera firmly enough in his hands and against his cheek regardless of the position of his body. In this manner, he can be sure of the greatest possible freedom to make quick changes in angle or position.

Lighting problems are quickly solved by photo-flood bulbs. With these as a source of light, it is naturally easier to be sure of the proper exposure if there is no additional, unmeasured light from the sky. In medical filming the background is usually without special interest so that its loss in the dark shadows beyond the radius of effective artificial lighting can give the subject a detached importance that will compare well with views taken in other rooms and on other occasions. Instructions with the lighting units are sufficient for the determination of the aperture in relation to the number and distance of the lights from the subject. All types of panchromatic black-and-white film register correct color values with this illumination, but color photography under the same circumstances demands a special type of film that is balanced for artificial light and sold for this purpose.

In attempting to take motion pictures indoors by natural light the value of "top light" must be appreciated, its absence in any room that is without large windows makes this type of motion-picture photography extremely unsatisfactory. A few older hospitals still have top-floor operating rooms beneath skylights, but the good north light that these have been planned to provide will give the only favorable conditions that one can ever expect to find for indoor natural-light photography. There may be a temptation to use direct sunlight for indoor photography, but it must be remembered that sunlight through the limited area of a window sash will give lines of shadow from the window frame and contrasting light and shadow on the subject with a spotlight effect unless something is done to lighten the shady side.

Greater interest in medical motion pictures is created by a change in the camera angle for variety. This does not refer to camera angles that distort perspective or overemphasize certain characteristics because it is imperative that medical motion pictures avoid "trick photography" and retain scientific accuracy. There is, however, no reason for the monotonous use of eye-level views when the camera man can walk around the patient to take successive views just as a visiting physician would do if he were given the same opportunity. Variation of the angle and position of the camera in this manner will make the film record more human and natural for the future edification of a medical audience.

A sprinkling of close-up views will also give greater satisfaction when associated with more

distant views of the whole subject. There is never a general view that does not contain a center of interest made so by its own arresting nature or by the subject of the demonstration. As soon as it is apparent that the audience will want to examine more closely, it is wise to be able to splice in a satisfactory close-up to show the details. The camera will then have done just what the average physician would have done if he had been in the presence of the patient. This feature may make the difference between success and failure when it comes to holding the attention of a medical audience.

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#### EDITING AND TITLING

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curiosity of future audiences. If the editor believes that this curiosity demands a close view, he should supply it, if it seems likely that a member of the audience unfamiliar with the material will want an explanation, he should place a title or a diagram at that point. Enough clinical data should be included in some manner along with the pictures to forestall any impression that the presentation is pointless. This all implies that the grouping of subjects should be tied together by a single theme either in the form of a discourse on one malady or as a frank presentation of the miscellaneous contents of a movie "scrapbook."

All films should be titled and edited before being shown to anyone except an occasional person who may have a direct interest in the care of the case. Complete editing means also that the material has been assembled according to plan, with the elimination of all unfit film as judged by any of the standards thus far discussed. Titling means the addition of written material or diagrams to supplement the pictures and round out the production into an understandable silent motion picture.

#### PROJECTION AT MEDICAL MEETINGS

Projection of medical motion pictures made by the private practitioner for his medical associates represents the goal of the entire endeavor of their making. The finished film, deftly shown to a comfortable audience, gives the hobby its greatest justification, but this seemingly simple matter has its problems and an excellent film may be made less effective by bad conditions at the time of projection. The medical photographer will probably find that in his locality the audiences made up of his professional colleagues will be of about the same size each time they gather. The size of the group and the room in which the pictures are shown may therefore become familiar factors. In an informal group it always pays to ask certain members to move into positions between the projector and the screen before the film begins, and it is better, if possible, to have the screen only slightly above natural eye level, even if it is necessary to provide a center aisle. The carrying case of the projector may sometimes serve as a stand for the machine to bring it that much higher than the ordinary table top so that the rays of light will hit the screen at right angles to its surface. The distance should be so adjusted that the picture will completely fill the reflecting surface within the black borders of the screen without overlapping onto the wall behind.

Although the room for projection must be darkened in some way, it is recognized that absolute darkness is usually unnecessary. Unavoidable sources of light should be shielded from the eyes of the audience, and beams of light must be prevented from hitting the screen to give unequal illumination of the darker parts of the pictures. When color film is shown, it is wise to have less light in the room and to be sure that what little remains is without decided color of its own to unbalance the colors in the pictures.

As pointed out above, if the medical motion-picture maker wishes to establish and preserve a reputation, he must consistently refrain from showing his pictures until completely prepared for projection. He should never be forced to provide running comment to explain his continuity or excuse defective photography unless he plans to have someone read a prepared script through a microphone to simulate a sound film. His handling of the projector should be quiet and not accompanied by false starts, flashes of light, delays or rewinds. He can accomplish a smooth beginning by starting the motor of the projector before turning on the light as the first title appears, and make a graceful ending by turning off the light before the blank strip runs through to give a blaze of light on the screen. The exhibitor should try to have his machine as quiet as possible by proper oiling, by straightening bent reels and by the use of a rubber pad under the machine if it is necessary to absorb the vibration. His table for projection should be solid, his electrical connections tight, and his projector gate and lens clean, and he should have everything in readiness before his audience arrives. All this care for detail will reap dividends in satisfaction, and an already theater-minded audience will wonder how an amateur could obtain such pictures.

#### SUMMARY

The groundwork for the production of creditable medical motion pictures by the private practitioner is discussed. The fact that motion pictures, as a field of medical expression, fall easily within the scope of a private practice is stressed. Any physician with simple equipment may obtain and use motion pictures to record his unique cases, because he has in his private practice the one vital thing necessary for such a visual record—the patient himself. No clinic or hospital has more than that.



of the face. A tripod is the standard means of securing steadiness for the camera. Other commercially made gadgets are available, but even without these assistants it should be possible for the photographer to hold the camera firmly enough in his hands and against his cheek regardless of the position of his body. In this manner, he can be sure of the greatest possible freedom to make quick changes in angle or position.

Lighting problems are quickly solved by photo-flood bulbs. With these as a source of light, it is naturally easier to be sure of the proper exposure if there is no additional, unmeasured light from the sky. In medical filming the background is usually without special interest so that its loss in the dark shadows beyond the radius of effective artificial lighting can give the subject a detached importance that will compare well with views taken in other rooms and on other occasions. Instructions with the lighting units are sufficient for the determination of the aperture in relation to the number and distance of the lights from the subject. All types of panchromatic black-and-white film register correct color values with this illumination, but color photography under the same circumstances demands a special type of film that is balanced for artificial light and sold for this purpose.

In attempting to take motion pictures indoors by natural light the value of "top light" must be appreciated, its absence in any room that is without large windows makes this type of motion-picture photography extremely unsatisfactory. A few older hospitals still have top-floor operating rooms beneath skylights, but the good north light that these have been planned to provide will give the only favorable conditions that one can ever expect to find for indoor natural-light photography. There may be a temptation to use direct sunlight for indoor photography, but it must be remembered that sunlight through the limited area of a window sash will give lines of shadow from the window frame and contrasting light and shadow on the subject with a spotlight effect unless something is done to lighten the shady side.

Greater interest in medical motion pictures is created by a change in the camera angle for variety. This does not refer to camera angles that distort perspective or overemphasize certain characteristics because it is imperative that medical motion pictures avoid "trick photography" and retain scientific accuracy. There is, however, no reason for the monotonous use of eye-level views when the camera man can walk around the patient to take successive views just as a visiting physician would do if he were given the same opportunity. Variation of the angle and position of the camera in this manner will make the film record more human and natural for the future edification of a medical audience.

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Physical examination was essentially unchanged. Complete neurologic examination revealed no abnormal signs other than those noted and recorded on admission. The total fluid intake and output, which were 2500 and 1148 cc. respectively, continued a normal course throughout the hospital stay.

On the 3rd day the temperature fluctuated between 100 and 104°F and the lower pole of the spleen became palpable. Daily blood smears taken at the peak of the fever and several taken after the administration of 1 cc. of adrenalin revealed no malarial parasites. X-ray studies of the skull and visual field examinations were essentially negative. The white-cell count remained under 10,000, and the differential count was within normal limits. The total serum protein was 6.4 gm per 100 cc., with an albumin of 4.7 gm, the albumin-globulin ratio being 2.8. An agglutination test for Brucella organisms was negative, and the results of the heterophil-antibody study were not yet known, the Beace-Jones protein was normal. Repeated throat smears and culture revealed beta-hemolytic streptococcus and *Staphylococcus aureus*. A blood specimen taken for culture was negative. The blood Kahn test was also negative.

On the 5th day the hemoglobin was 15 gm. per 100 cc. and the white-cell count 6700, the differential count being within normal limits, but an occasional blood cell resembling the lymphocytic series and believed to be a polymorphocyte was seen. A sternal puncture revealed essentially normal bone marrow.

From the 6th to the 15th hospital day the white-cell counts began to rise and fluctuate between 13,000 and 22,150, the differential counts revealing 83 to 98 per cent lymphocytes, 10 or 15 per cent of which were polymorphocytes and 1 or 2 per cent so immature that they were difficult to differentiate from lymphoblasts. At least 5 per cent of the lymphocytes had fenestration and heavy nuclear, chromatin network. The peroxidase stain was negative.

On the 11th hospital day the heterophil antibody titer was 1:448. The blood specimen for this examination had been drawn on the 4th hospital day.

The repeated blood examinations, which revealed the lymphocytosis and fenestrated lymphocytes the abnormal heterophil-antibody titer the palpably enlarged spleen the absence of anemia and the normal bone-marrow study substantiated the diagnosis of infectious mononucleosis.

To aid the patient during the period of extreme lymphocytosis 40,000 units of penicillin was administered every 4 hours, and large doses of components of the vitamin B complex were given orally. Pyridoxine for intravenous use was not available.

The patient continued to run a low-grade intermittent fever, and on the 13th hospital day, while still on penicillin therapy, he developed an acute bilateral, lacunar tonsillitis. The temperature, however, never rose above 100°F. Within

3 days the throat signs and symptoms began to recede, and the temperature returned to normal and remained so until discharge from the hospital.

During the entire hospital stay, the patient was given complete neurologic examinations daily, but no disease other than that noted and recorded on admission was discovered. From the 18th hospital day until the 31st hospital day, the spleen gradually receded in size, until it was not palpable 7 days before discharge. A blood study on the 28th hospital day revealed that the lymphocytes were shifting back toward a normal percentage but were still 69 per cent, the neutrophils 25 per cent, the monocytes 3 per cent and the eosinophils 3 per cent. The papilloretinal edema had almost completely subsided.

On the 31st hospital day the patient was discharged feeling and looking well. The papilloretinal edema had completely disappeared, and the spleen was no longer palpable. The heterophil antibody titer was still 1:448 but the white-cell count was 6000 with 50 per cent lymphocytes and 50 per cent neutrophils no unusual white cells were apparent.

### SUMMARY

An unusual case of infectious mononucleosis with a complicating bilateral papilloretinal edema is presented. The history and physical findings suggested a variety of conditions, but the laboratory data and the course confirmed the proper diagnosis.

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## MEDICAL PROGRESS

### SERUM LIPIDS AND THEIR VALUE IN DIAGNOSIS (Concluded)\*

SIEGFRIED J THANNHAUSER, M D †

BOSTON

#### *Normocholesteremia and Foam-Cell Formation*

*Increased xanthoma formation in essential xanthomatosis of the normocholesteremic type* This condition is synonymous with Schüller-Christian disease, lipid granulomatosis, eosinophilic granuloma and eosinophilic xanthomatous granuloma. Pinkus and Pick<sup>87, 88</sup> were the first to discover that the fat substances in the foam cells are cholesterol and cholesterol esters. These authors advanced the theory that cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood. In the syndrome under discussion, xanthoma-cell formation occurs without increased cholesterol supply from the blood — that is, with normal cholesterol values in the serum. Waldeyer<sup>86</sup> has already suggested that the xanthoma cell is an embryonal cell capable of forming different kinds of lipids, which are retained within the cell and released only by disintegration of these cells. Since reticulum cells and histiocytes may retain the functional possibilities of embryonal cells, it can be assumed that they are also capable of forming various kinds of lipids including cholesterol. It is conceivable that in these cells an inherent metabolic potentiality or a disturbance of the intracellular enzymatic systems concerned with the formation of cholesterol results in an accumulation of cholesterol within the cells, thereby transforming them into xanthoma cells (foam cells). It may be understood that under these abnormal conditions the excess of cholesterol found is retained within the cell and is not released into the blood stream. Such an explanation was applied by Thannhauser and Magendantz<sup>43, 44</sup> to the pathology of a systemic disorder showing xanthomatous and granulomatous features, which they designated as "primary essential xanthomatosis of the normocholesteremic type," singling out the normal cholesterol content of the serum as the leading clinical sign for differential diagnosis.

It was emphasized by these authors that certain organs may be involved singly or in various combinations in this systemic disease. The organs that may be affected are the skin (disseminated type of xanthomas), osseous system, dura, brain, lungs, pleura, liver, spleen and lymph nodes.<sup>43, 44</sup> Involvement

of the dura, brain and osseous system is known as Schüller-Christian syndrome.<sup>89</sup> Rowland,<sup>90-92</sup> Chester<sup>93</sup> and Fraser,<sup>94</sup> in their pioneer work on the histology of the xanthomatous lesion in Schüller-Christian syndrome, had already demonstrated clearly that this lesion is granulomatous in nature (lipid granulomatosis). The presence of numerous eosinophils, as well as histiocytes and reticulum cells, in the granulomatous tissue had already been observed by these authors. These early investigators were, however, more impressed by the nests of foam cells in the granulomatous lesions than by the eosinophils and histiocytic elements and therefore designated the lesions as "xanthomatous" and the disease as "lipid granulomatosis" or "cholesterol granulomatosis." Ceelen,<sup>95</sup> in 1933, and Gerstel,<sup>96</sup> in 1934, suggested that the systemic granulomatous process is the primary feature of the disease, whenever foam cells appear in later states. In 1940 Lichtenstein and Jaffee<sup>97</sup> reported cases of solitary bone lesions of this disease. Fraser<sup>94</sup> had previously published cases with solitary bone lesions in an excellent and detailed study, describing and picturing the main histologic features of the lesions — namely, the reticulohistiocytic proliferation, the increase of eosinophilic cells in the granulomatous tissue and the gradual development of foam cells in the lesion. He designated such bone lesions as "lipoid granulomas." Lichtenstein and Jaffee apparently believed that this type of granuloma was a disease not hitherto described and named it "eosinophilic granuloma." It was not until the studies of Farber<sup>98-100</sup> and Engelbreth-Holm, Teilum and Christensen<sup>101</sup> that the designation "eosinophilic granuloma" was applied not only to single bone lesions but also to those of the Schüller-Christian syndrome, as well as to the generalized lesions in other organs of the group clinically classified by Thannhauser and Magendantz<sup>43</sup> as "essential xanthomatosis of the normocholesteremic type." Through the studies of Teilum and his co-workers it was histologically demonstrated that the natural history of such an eosinophilic granuloma comprised the following different phases: a proliferative phase in which reticulohistiocytic proliferation associated with accumulation of eosinophilic leukocytes is observed — in this phase there is no evidence of foam cells, a granulomatous phase, with increase of blood vessels and fibrils, reticular cells and histiocytes, eosinophils and giant cells (Touton cells) and incipient lipid phagocytosis, a xanthomatous phase,

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with nests and isolated foam cells, and a fibrous stage, considered to be evidence of healing. These four phases often show no strict demarcation during the course of the disease, and their histologic features may overlap considerably during the course of the disease. The paper of Lichtenstein and Jaffee<sup>17</sup> has caused considerable misunderstanding about the classification of the disease under discussion, as is obvious from recent publications such as that of Weinstein and his associates.<sup>18</sup> It is evident that solitary eosinophilic granuloma is the monosymptomatic early stage of a systemic disease designated by Fraser<sup>11</sup> and Chester<sup>12</sup> as lipid granulomatosis, by Rowland<sup>19-22</sup> as Schuller-Christian disease and by Thannhauser and Magendanz,<sup>23, 24</sup> from the clinical point of view, as essential xan-

thomatous increase of the normal constituents of this tissue, presupposing that a large specimen of this organ is used for the quantitative chemical analysis. For this reason, the quantitative analysis of a tissue specimen will not show a considerable increase of cholesterol originating from detritus of microscopic areas of focal necrosis, since the increase of cholesterol in one cell is balanced by the loss of cholesterol from another cell, which has previously undergone dissolution.

The quantitative chemical analysis of 0.5 to 2 gm of tissue in the xanthomatous phase of eosinophilic xanthomatous granuloma shows an increase of ten to twenty times in the quantity of cholesterol as compared with the content of a piece of normal organ of similar weight. These

TABLE 3 Lipid Partitions in Specimens of Tissue during the Xanthomatous Phase of Eosinophilic Xanthomatous Granuloma.

Tissue	TOTAL CHOLESTEROL %	FREE CHOLESTEROL %	CHOLESTEROL ESTERS %	TOTAL PROSTHOLIPID %	SPHINGO- MYELIN %	LECITHIN	TOTAL FATTY ACID	NEUTRAL FAT
Diseased lymph node <sup>1</sup>	17.90	2.20	15.70	6.4	Trace	—	—	—
Normal lymph node	0.60-2.30	0.50-1.10	0.20-1.20	5.5-11.0	0.5-4.0	—	—	—
Dura mater <sup>10</sup>	18.58	3.20	15.30	—	—	1.6	—	—
Skin <sup>10</sup>	4.55	3.66	0.89	—	—	—	3.64	—
Normal skin	0.15-0.30	—	—	—	—	—	9.05	0.71
Diseased liver <sup>1</sup>	7.25	4.55	2.0	7.4	—	—	8.60-13.0	1.4-4.0
Normal liver	1.10-2.60	1.50-2.10	0.45-0.55	9.0-11.0	—	—	—	—

thomatosis of the normocholesteremic type. All these authors refer to the same disease. The designation of the disease in question as eosinophilic xanthomatous granuloma satisfies the clinical and the histologic observations, even if such a classification does not embrace the proliferative reticulohistiocytic phase.

The recent histologic studies of Farber<sup>25-100</sup> and especially of Teilmann<sup>101</sup> contributed to a better understanding of the histology of the lesion. There is, however, an important point in which one may differ from the interpretation of Farber,<sup>10</sup> who does not regard xanthoma-cell (foam-cell) formation as one of the pathognomonic features of the lesion. He implies that the xanthoma cell, if present in the granulomatous tissue, develops by cholesterol infiltration into the cells. Cholesterol should originate from the detritus of focal necrosis and should be locally absorbed and stored by the macrophages. The following objections may be raised against this interpretation.

A considerable increase of a normal chemical constituent of a tissue can be the result of an infiltration of this substance into the cells due to an increased supply from the blood stream or of an increased formation of this substance within the cells of the tissue. A shift of a chemical cellular constituent from one cell, which has supposedly undergone dissolution, to another cell macrophagic in character will not cause a meas-

urable increase of the normal constituents of this tissue, presupposing that a large specimen of this organ is used for the quantitative chemical analysis. For this reason, the quantitative analysis of a tissue specimen will not show a considerable increase of cholesterol originating from detritus of microscopic areas of focal necrosis, since the increase of cholesterol in one cell is balanced by the loss of cholesterol from another cell, which has previously undergone dissolution. The enormous increase of cholesterol in the analyzed specimens of tissues during the xanthomatous phase of eosinophilic granuloma must originate in the organ itself as a result of increased cholesterol formation within certain cells capable of cholesterol synthesis. These cells, mostly of reticular and histiocytic origin, form and retain cholesterol, gradually developing the features of foam cells. The data presented in Table 3 illustrate this interpretation.

Xanthoma disseminata of the skin, the lesion characteristic of this group of xanthomatous granuloma, does not undergo visible necrosis, and microscopical examination reveals no extensive foci of necrosis, which could explain the extensive development of foam cells in the lesion.<sup>101, 102</sup>

Granulomatous lesions of the skin — like those in Hodgkin's disease, mycosis fungoides and infectious granuloma — show large areas of necrotizing processes even with macroscopically visible ulceration but no foam-cell formation. It is not understood why foam cells should arise only from the detritus of cells in eosinophilic

xanthomatous granuloma when they do not originate from the detritus of other granulomatous lesions in which large areas of necrosis are present. It is therefore unlikely that xanthomatous cell formation in the xanthomatous phase of eosinophilic xanthomatous granuloma is an accidental occurrence originating from the debris of local necrosis. It is, rather, suggested that during the abundant proliferation of reticulum cells and histiocytes in the earlier phases of the disease, cells that have preserved the inherent ability of the embryonal reticulum fat cell to synthesize and retain cholesterol within the cell arise and thus develop in a later phase into xanthoma cells (foam cells).<sup>66</sup>

Farber<sup>98</sup> states that he is not willing to accept the classification of Schüller-Christian syndrome in the group of lipid metabolic disorders. One can only agree with this consideration so far as this syndrome is not caused by a general disturbance of the *intermediary* cholesterol metabolism. For the consideration discussed above, it may be assumed that in the course of granuloma formation in the disease under discussion cells mainly of reticular and histiocytic origin intrinsically accumulate cholesterol as a result of an inherent metabolic potentiality or an intracellular metabolic disorder. These cells, which gradually develop the features of foam cells, are as pathognomonic in the later phases as the accumulation of eosinophilic cells is in the early stages of the disease. The evidence at present points to a formation of cholesterol within the cell rather than cholesterol infiltration for the explanation of the mechanism of xanthoma-cell formation in eosinophilic xanthomatous granuloma. For clinical considerations, however, the normal cholesterol content of the serum in this syndrome is an important feature for the differential diagnosis from other types of xanthomatoses.

*Local accumulation of foam cells.* A local accumulation of foam cells is occasionally encountered in inflammatory tissue or in a tumor growth, as in osteomyelitis, osteitis fibrosa, cystica disseminata, xanthomatous transformation of the mesentery and xanthoma cells in tumors. The serum cholesterol in such cases is normal. The mechanism of an occasional foam-cell development in a local, small, well defined area is not yet clarified.

#### LABORATORY PROCEDURES

The extraction of serum or wet tissue, according to Bloor,<sup>106</sup> is the basis of the determination of the total lipids and of the lipid fractions. This precedes all other analytic procedures. In the method for the determination of the total phospholipids the alcohol-ether extract is evaporated to dryness under reduced pressure or in an atmosphere of nitrogen, the dry residue is extracted with a small amount of petroleum ether from which the phospholipids can

be precipitated by acetone and magnesium chloride and determined oxydimetrically after treatment with chromic acid. In this laboratory we prefer to determine the total phosphorus directly in the petroleum ether extract because the results obtained with this technic are not influenced by the presence of cerebrosides. Gortner<sup>107</sup> also concludes that the results obtained with phosphorus determination are more consistent than those obtained with the oxydimetric methods.

Folch and Van Slyke<sup>108</sup> described a different extraction procedure for the plasma lipids by which certain disadvantages of Bloor's procedure, such as the contamination of the final petroleum ether extract with nonlipid substances, can be avoided. The lipids are precipitated together with the proteins by colloidal iron in the presence of magnesium sulfate. Finally, they are extracted from the washed precipitate by an alcohol ether mixture at room temperature. In the event that one wishes to determine the lipids and their fractions in dry tissue, small pieces of the fresh material are immersed in ether cooled with solid carbon dioxide. The frozen pieces are dried in a vacuum desiccator over phosphorus pentoxide.

Various analytical procedures for the quantitative estimation of the phosphatide fractions have been devised. When they are combined with the determination of the total phospholipids, a fairly complete quantitative partition of a given phospholipid mixture is obtained. It should be pointed out, however, that the results obtained with different schemes of the partition show some discrepancies that cannot yet be completely explained. One of the difficulties encountered in this field arises from the necessity of hydrolyzing the lipids prior to the chemical analysis. Despite the fact that the general behavior of the lipids toward hydrolyzing agents is fairly well known, the conditions required for the quantitative hydrolysis of individual components of the various fractions have not as yet been studied sufficiently to exclude errors due to incomplete hydrolysis.

#### Phospholipids

The amount of amino nitrogen in phospholipid mixtures corresponds to the total amount of cephalins. The Van Slyke method is therefore widely used for the determination of cephalin in phospholipid mixtures. It must be emphasized, however, that unsaturated fatty acids evolve considerable amounts of inert gas with nitrous acid.<sup>108</sup> Folch, Schneider and Van Slyke<sup>109</sup> found negligible amounts of cephalin in the serum lipids when they took the precaution of hydrogenating the lipids before the determination of the amino nitrogen. Entenman and Chaikoff<sup>110</sup> obtained similar results by means of choline determinations in the plasma lipids. It appears that amino nitrogen determinations in the lipid mixtures should be carried out after the

Removal of the fatty acids by a suitable method of hydrolysis

A micromethod for the determination of the two known component nitrogen groups of cephalin—namely, ethanolamine and serine—has recently been reported by Artom.<sup>111</sup> It is based on the quantitative liberation of the nitrogen of either substance in the form of ammonia during the oxidation with periodate. When this method is combined with the quantitative separation of both substances by the selective adsorption of colamine on permute, the amounts of either substance can be determined. In many tissues the sum of ethanolamine and serine as determined according to Artom's method agrees with the values for the total cephalin obtained by other methods. In some organs, such as the brain, kidneys and lungs, the figures obtained with the periodate method are too high, probably owing to the presence of sphingolipids in considerable amounts. It should be mentioned that Artom found considerable amounts of cephalins in blood plasma, contrary to the results obtained with some of the techniques reported above. Blix<sup>112</sup> estimated cephalin in determining choline in hydrolysates of phospholipids by vacuum distillation under a pressure equivalent to 10 mm of mercury at 75 to 80°C and following acidimetric titration.

The sum of the choline-containing phospholipids (lecithin and sphingomyelins) can be estimated by the determination of the choline obtained after refluxing the lipid mixture for two hours with saturated barium hydroxide.<sup>113</sup> The best method for the determination of choline appears to be the spectrophotometry of its reineckate in acetone solution.<sup>114</sup> Amounts between 50 and 400 microgm can be determined with an error of 5 per cent.

Taurog and his co-workers<sup>115</sup> achieved the separation of the choline-containing from the noncholine-containing phosphatides of liver by adsorption of the total phosphatides on magnesium oxide and selective elution of the choline-containing phospholipids by methanol.

The sum of the glycerol-containing phosphatides (lecithin and glycerol cephalins) is obtained by glycerol determinations in the dried phospholipid fractions, according to Blix.<sup>116</sup>

Attempts have been made to determine the glycerol in lipid extracts by periodate oxidation.<sup>117</sup> The application of this principle to the analysis of fats appears to give reliable results. In the analysis of phospholipids, the use of periodate for the analysis of glycerol encountered two serious difficulties: the presence in the hydrolysate of interfering substances such as colamine and serine and the fact that the usual procedures for the hydrolysis of phospholipids do not lead to the liberation of glycerol as such but to the formation of a mixture of alpha and beta glycerophosphoric acid, the latter not reacting with periodate and thus escaping determination. It should be emphasized that

alpha and beta glycerophosphate, rather than glycerol, should be used as test substances whenever procedures for the determination of glycerol in phospholipid mixtures are to be checked.

A convenient micromethod for the quantitative partition of phospholipid mixtures into monophosphatides and sphingomyelin has been developed by Schmidt et al.<sup>118</sup> When lecithin or cephalins are incubated with nitrogen and potassium hydroxide at 37°C. for fifteen hours, the total amount of their phosphorus groups become soluble in dilute acids, whereas the phosphorus of sphingomyelin remains insoluble under these conditions.

A direct microdetermination of sphingomyelin as acetone-insoluble reineckate has been described by Thannhauser, Benotti and Reinstein.<sup>119</sup> The sphingomyelin reineckate includes that of hydrolecithins, which have recently been found to be present in several tissues of brain and lung. Representative figures of the concentration of phospholipids in various tissues<sup>120</sup> and in isolated nuclei<sup>121</sup> have been reported by several authors.

### Cerebrosides

A method for the determination of cerebrosides has been developed by Brückner.<sup>122</sup> It is based on the colorimetric determination of galactose by means of orcinol and sulfuric acid in the hydrolysate of the lipid extracts. So far as specificity is concerned, it is superior to the earlier reductometric methods<sup>123</sup>; it should be mentioned, however, that Brückner's method cannot be applied to the determination of cerebrosides found in organs in Gaucher's disease.

Ottenstein, Schmidt and Thannhauser<sup>124</sup> have devised a method to determine galactosidocerebrosides and glycosidocerebrosides in organs that may contain both varieties of cerebrosides.

### Cholesterol and Cholesterol Esters

Many methods of estimating total cholesterol and cholesterol esters have been published. The procedure of Schoenheimer and Sperry<sup>125</sup> requires more time than other methods but is the most reliable one for clinical use.

### Total Lipid Fatty Acids

The total fatty acids in lipid mixtures are best determined by the method of Stoddard and Drury.<sup>127</sup>

### Neutral Fat

There is no reliable method for the direct estimation of neutral fat (glycerol fatty acid esters) in lipid mixtures that contain other fatty acid esters like phosphatides and cholesterol esters. One must therefore determine the total fatty acids in a lipid mixture and subtract from the value obtained the quantity of fatty acids contributed by both the total phospholipids and the cholesterol esters. The remainder, when multiplied by 1.04, represents

TABLE 4 Serum Analyses of Lipids in Various Diseases

CONDITION	TOTAL CHOLESTEROL mg/100 cc	CHOLESTEROL ESTERS % total cholesterol	FREE CHOLESTEROL mg/100 cc	TOTAL PHOSPHOLIPIDS mg/100 cc	LECITHIN mg/100 cc	SPHINGO MYELIN mg/100 cc	TOTAL FATTY ACIDS mg/100 cc	NEUTRAL FAT mg/100 cc	REMARKS*
Normal values	150-260 350-800	70-75 Normal	40-70 100-250	150-250 250-430	100-200 220-400	10-30 Normal	200-450 500-900	0-150 Normal	Serum transparent, no increase in neutral fat, total fatty acids elevated because of high cholesterol esters and phospholipids, tuberos and plain skin xanthomas, tendon xanthomas and atheromas of blood vessels
Xanthomatous biliary cirrhosis	800-2200	Normal	240-640	800-2000	770-1950	30-50	1000-2500	0-60	Serum transparent, no increase in neutral fat, total fatty acids elevated because of high cholesterol esters and phospholipids, jaundice of years' duration in later stages total cholesterol decreases and ratio of cholesterol to cholesterol esters drops
Essential xanthomatosis, normocholesteremic type (eosinophilic xanthomatous granuloma)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Xanthoma disseminata of skin and cosmophilic xanthomatous granulomas of dura, brain, lung, osseous system, liver, spleen and lymph nodes occur singly, in various combinations or as a generalized form of the disease, no jaundice
Idiopathic (familial) hyperlipemia, with hepatosplenomegaly and secondary xanthomatosis	300-600	60-75	90-180	260-500	240-420	Normal	2000-4000	1000-3500	Serum creamy, occasionally eruptive secondary xanthomas, influenced by diet
Idiopathic hyperlipemia occasionally associated with slight diabetes	300-600	60-75	90-180	260-500	240-420	Normal	2000-4000	1000-3500	Serum creamy, severe degree of secondary eruptive xanthomas, influenced by diet
Hyperlipemia associated with severe diabetes and secondary xanthomatosis	300-600	60-75	90-180	260-500	240-420	Normal	1500-3000	500-2000	Serum creamy, secondary eruptive xanthomas influenced by insulin
Hyperlipemia in chronic pancreatitus, with secondary xanthomatosis	300-600	60-75	90-180	260-500	240-420	Normal	1500-3000	500-2000	Serum creamy, rarely secondary xanthomatosis, occasionally slight diabetes, other symptoms of pancreatic disease present, influenced by diet
Hypercholesteremia associated with hypothyroidism	300-600	Normal	90-180	250-400	220-380	Normal	500-800	100-150	Serum transparent, rarely secondary xanthomatosis, influenced by thyroid and diet
Hyperlipemia in lipid nephrosis	400-800	Normal	120-250	250-400	220-380	Normal	500-1000	150-400	Serum slightly milky, no secondary xanthomatosis, low serum protein
Localized foam-cell formation (osteomyelitis, osteitis fibrosa cystica disseminata and xanthomatous mesenteric)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Serum transparent
Gaucher's disease	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Reticulum cells and histiocytes of bone marrow, spleen, liver and lymph nodes contain large amounts of glycoside cerobrosides, pigmentation in patches not present in all cases, infantile Gaucher's disease in generalized form and lesions are present in all organs
Niemann-Pick disease	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Reticulum cells and histiocytes of all organs contain large amounts of sphingomyelin, cherry-red spot in macula of retina, observed in infants — rare in persons over two years
Tay-Sachs disease (amaurotic idiocy)	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal	No increase of sphingomyelin in organs, ganglionides increased in brain cherry red spot in macula of retina
Hepatitis	260-400 300-400 Less than 100	40-60 30-40 10-30	100-260 210-280 70-80	Normal Low normal Lower than 100	Normal Normal Lower than 100	Normal Normal Low	Normal Normal Normal	Normal Normal Normal	Repeated estimations of the total cholesterol and of the ratio of cholesterol to cholesterol esters during the course of the hepatitis are helpful in the establishment of the prognosis of this disease
Acute	350-400	60-70	Normal	Normal	Normal	Normal	Normal	Normal	In contrast to hepatitis, the cholesterol esters remain in the first stages of occlusion on the borderline of normal after a few weeks of occlusion the cholesterol esters decrease, being a sign of hepatocellular damage
Chronic	400-500	40-50	200-300	Normal	Normal	Normal	Normal	Normal	
Acute-yellow-atrophy type	260-400	40-60	100-240	Normal	Normal	Normal	Normal	Normal	
Complete obstruction of common bile duct by stone or tumor	260-400	40-50	130-240	150-400	110-370	Normal	Normal	150-500	
Acute	Less than 100	10-40	10-60	Low normal	Low normal	Normal	Normal	50-300	In conditions of liver insufficiency serum may be normal but fatty acids are normal but neutral fat may be increased
Biliary cirrhosis	Less than 100	10-40	10-60	Low normal	Low normal	Normal	Normal	50-300	
Compensated portal cirrhosis	Less than 100	10-40	10-60	Low normal	Low normal	Normal	Normal	50-300	
Alcoholic cirrhosis complicated by hepatitis and fatty liver	Less than 100	10-40	10-60	Low normal	Low normal	Normal	Normal	50-300	
Liver insufficiency of varied etiology	Less than 100	10-40	10-60	Low normal	Low normal	Normal	Normal	50-300	

\*Cerebrosides are not present in the serum in any of these diseased conditions

neutral fat.<sup>8</sup> The formula for the evaluation of neutral fat is as follows

$$\left[ \text{Total fatty acids (mg. per 100 cc.)} - \left[ 0.72 \text{ cholesterol esters (mg. per 100 cc.)} + 0.69 \text{ total phospholipid (mg. per 100 cc.)} \right] \right] \times 1.04 = \text{neutral fat (mg. per 100 cc.)}$$

The factors 0.72 and 0.69 assume an average fatty acid molecular weight of 277. Erroneously, the value obtained for total fatty acids is often taken as equal to the value of neutral fat. For these reasons the values of neutral fat reported in the literature are mostly too high. In cases in which the cholesterol present as esters and phospholipids is high in the serum, the error is great.

It can easily be seen that by a suitable combination of several of the procedures discussed above it is possible to achieve a rather complete quantitative partition of the phospholipids. It must be emphasized, however, that the accuracy of figures obtained by calculating a difference should be carefully examined in each case. Only in tissues are the total lecithin and total cephalin fractions so large that errors of the individual determinations do not seriously interfere with the calculation of the difference.

In the laboratory of the Joseph H. Pratt Diagnostic Hospital the following procedures are adopted in the routine determination of lipids in the serum for diagnostic purposes

For the determination of total cholesterol, free cholesterol and cholesterol present as esters the method of Schoenheimer and Sperry<sup>12</sup> is used. The only important change from the original method consists in the extraction of 1 cc. of serum in 25 cc. of acetone and alcohol (1:1).<sup>13</sup>

The total phospholipids, the sum of lecithin and cephalin and the sphingomyelin are estimated by the procedure of Schmidt et al.<sup>14</sup>

The total fatty acids are determined by the method of Stoddard and Drury.<sup>15</sup>

Neutral fat is evaluated from the figure obtained for total fatty acid minus the fatty acids present in cholesterol esters and phospholipids, according to the formula of Thannhauser and Reinstein.<sup>8</sup> For the evaluation of neutral fat it is therefore necessary to determine the total fatty acids, cholesterol esters and total phospholipids.

The normal values of lipids in serum, expressed in milligrams per 100 cc., with these methods are as follows

Total cholesterol	150 to 260
Free cholesterol	40 to 70
Cholesterol esters	105 to 195*
Total phospholipids	150 to 250
Saponifiable phospholipids (lecithin and cephalin)	110 to 230
Sphingomyelin	10 to 30
Total fatty acids	200 to 450
Neutral fat	0 to 150
Cerebrosides	0

\*Seventy to 75 per cent of total cholesterol.

Table 4 presents the results of serum analyses of lipids in various diseases

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 33411

#### PRESENTATION OF CASE

A seventy-year-old widow was admitted to the hospital because of "feeling very bad."

One week prior to admission the patient found herself unable to get out of bed one morning and complained of weakness and pain in the legs. She also noted occasional twinges of pain across the chest, lasting only a few minutes. These symptoms persisted until the time of admission and added to them was increasing shortness of breath. There was no severe pain, paroxysmal dyspnea or cough. There was said to have been some fever at the onset of the present illness, but no chills had been noted. The patient had always been in good health until four years before admission when she developed diabetes, which was controlled by diet and insulin. One year before admission she was seen in the Out Patient Department for scabies. A medical check-up at that time uncovered a history of some dyspnea and ankle edema, and on physical examination the blood pressure was 150 systolic, 90 diastolic. The heart was not enlarged, but a gallop rhythm was heard, there was slight pitting edema of the ankles and occasional rales at the lung bases. No digitalis was given, and the diabetes was controlled with a diet and 12 units of protamine-zinc insulin daily.

There was no history of hypertension, angina, intermittent claudication or orthopnea. The weight had remained stationary.

Physical examination revealed a pale woman lying flat in bed. There were many old retinal hemorrhages. The neck veins were distended and pulsating.

There were moist rales at both lung bases. The heart was enlarged, the area of dullness extending to the anterior axillary line, the rhythm was regular, with occasional extrasystoles, the sounds were somewhat distant, and to the left of the sternum in the fourth interspace was a rough, high-pitched sound, obscuring the first heart sound. This was believed to be a friction rub. The abdomen was protuberant but tympanitic in the flanks. The liver edge was felt one handbreadth below the costal margin and was firm and nontender. The spleen was enlarged to percussion. The ankle jerks and knee jerks were absent, and vibration sense was probably absent.

The temperature was 101.4°F, the pulse 90, and the respirations 28. The blood pressure was 130 systolic, 70 diastolic.

The urine gave a + test for albumin, a brown test for sugar and a + test for acetone, the sediment was normal. The hemoglobin was 10 gm per 100 cc., and the white-cell count 9500, with 85 per cent neutrophils. The serum protein was 7.26 gm per 100 cc., with an albumin-globulin ratio of 1.21, the van den Bergh reaction was 0.9 mg. per 100 cc. direct and 1.1 mg. indirect, and the cephalin flocculation test was + in twenty-four and +++ in forty-eight hours, the cholesterol was 181 mg., the cholesterol esters 100 mg., the nonprotein nitrogen 50 mg., and the fasting blood sugar 227 mg per 100 cc. The carbon dioxide was 25.4 milliequivalents per liter.

An x-ray film of the chest showed a heart shadow greatly enlarged in all diameters. There was fluid in the pleural sinuses, and the lung roots and markings were prominent (Fig. 1). A film of the abdomen showed a large gallstone in the right upper quadrant and a shadow in the left upper quadrant compatible with an enlarged spleen.

An electrocardiogram showed sinus tachycardia, a rate of 120 and a PR interval of 0.12 second, with an elevated ST segment in Lead 1 and a depressed ST segment in Lead 3. The T waves were upright in Leads 1 and 2, flat in Lead 3 and upright in Leads CF<sub>1</sub>, CF<sub>4</sub>, and CF<sub>6</sub>, the complexes in the limb leads were low.

The course continued to be febrile, the temperature swinging from 101 to 103°F. On the second hospital day the heart rate became regular again at a rate of 90. The friction rub disappeared. In spite of digitalis, quinidine, insulin and oxygen the patient did poorly. On the fourth hospital day the breathing became Cheyne-Stokes in character, the neck veins became more distended, and the chest was filled with moist rales. There was no tenderness or swelling of the legs. The white-cell count was 15,500, with 95 per cent neutrophils. The temperature rose to 103.5°F, the nonprotein nitrogen was 88 mg. and the fasting blood sugar 407 mg per 100 cc., and the carbon dioxide was 26.2 milliequivalents per liter. On the fifth hospital day the temperature rose to 104°F, and the patient became unresponsive.

breathing rapidly. The heart sounds were distant and regular, the blood pressure was 110 systolic, 60 diastolic, and a paradoxical pulse was noted. Later during the same day the patient died.

#### DIFFERENTIAL DIAGNOSIS

DR CHARLES L. SHORT: May we see the x-ray films?

DR STANLEY M. WYMAN: This first film and the next film taken three days later show a grossly enlarged heart. Both films were taken with the patient in the supine position so that the exact size cannot be measured. There is no characteristic configuration. There is calcification in the region of the aorta, and in the lateral view the calcified area is seen descending in the chest. There is no gross dilatation of the pulmonary vessels. I cannot be sure of fluid in the pleural cavities, and it is impossible to exclude the possibility of fluid in the pericardial cavity. The patient has had an old fracture of the ribs, which I do not believe to be of any significance. The last film shows a gallstone, or an area of calcification described as being consistent with gallstone. It is difficult to see what is described as an enlarged spleen. I believe that the



FIGURE 1

spleen comes down to this point and is not definitely enlarged. I see no definite gas in the biliary radicles. There are no evident dilated loops of bowel.

DR SHORT: Is much pulmonary congestion apparent?

DR WYMAN: I should say that there is very little x-ray evidence.

DR SHORT: No more than what one might expect with a heart of that size?

DR WYMAN: The superior vena cava looks more prominent on the second film than on the first film, suggesting some degree of right ventricular failure.

DR SHORT: There is no question about one diagnosis in this patient—that is, the diabetes. This was at first mild and easily controlled with small doses of insulin, but at the time of admission it was resistant. At that time the patient had mild acidosis without appreciable lowering of the carbon dioxide. As a complication of diabetes she had evidence of retinopathy and probable peripheral neuritis, suggested by the weakness in the legs, the pain in the extremities and the absent reflexes. We must look beyond the diabetes, however, for the actual cause of death. It also seems clear that there had been some cardiac failure for at least a year and that at least some of the signs and symptoms of congestive heart failure had developed during the terminal illness. In addition, the fever and the leukocytosis suggest the presence of an infectious process at the time of and shortly before death. I think that we must first decide whether or not it is necessary to look outside the heart to explain the terminal illness. There was increasing nitrogen retention during the hospital stay. Were any further urine specimens available?

DR TRACY B. MALLORY: Three urine examinations were done, of which two revealed no cells in the sediment and the other disclosed only one or two white cells per high-power field. Albumin was present in all in small amounts.

DR SHORT: Certainly, from the urine examinations, we cannot decide that the patient had pyelonephritis. I am thinking especially of the type that is frequently found in diabetes: necrotizing renal papillitis. This diagnosis should be considered in any diabetic patient dying with evidence of urinary infection and progressive nitrogen retention. But, in the absence of pus in the urine, I do not believe that it is possible to make that diagnosis, and in any case it would not explain the findings in the chest.

The enlarged liver and the probably enlarged spleen, together with a very slight degree of jaundice, draw attention to the liver. There was also a slight depression of the serum albumin and a positive cephalin-flocculation test. It seems, however, that in the presence of both diabetes and heart disease more positive evidence is needed before liver disease can be regarded as either a primary or a secondary cause of death.

We are left to determine the type of cardiac disorder present—one accompanied by high fever and by a pericardial friction rub. Rheumatic carditis and pericarditis are possible at any age, although they seem unlikely in this patient, especially in the absence of any characteristic murmur. Acute isolated myocarditis, or Fiedler's myocarditis, is a rare cause of cardiac enlargement and failure, usually accompanied by fever. Since I should need more

extensive electrocardiographic changes to make that diagnosis, I shall mention it only in passing, along with another type of heart disease with fever—abscess in the myocardium. Coronary disease, which is common in both male and female patients with diabetes, must of course be considered. That may have accounted for the cardiac failure a year before admission and for the terminal illness in the form of an acute infarction. There are certain features against the diagnosis of coronary infarction in this patient, however. The pain in the chest was not characteristic. There was no marked fall in blood pressure. The electrocardiogram is not specific for recent infarction in view of the normal anterior-chest leads, although the slight changes may be accounted for by a previous infarction in another region of the heart. The height of the fever would be unusual in coronary infarction unless there were involvement of an extensive area of the heart. I therefore doubt that an acute coronary infarction was the cause of death. Of course, the height of the fever may be explained by a lesion elsewhere in the body, especially pulmonary infarction, but we have no evidence in its favor. A more appealing diagnosis to me is pericarditis of a purulent nature, which is a rash diagnosis to make in the absence of sepsis elsewhere or in the absence of pneumonia. As Dr Wyman has pointed out the x-ray studies are consistent with pericardial effusion. The friction rub is also consistent, as are probably the electrocardiographic changes. There are some atypical features about the patient that are helpful. When she came in she could lie down flat in bed, and as Dr Wyman pointed out, there is very little x-ray evidence of congestive failure. This diagnosis would explain the high fever and, I believe, the other aspects of the case, except for the nitrogen retention, and I should therefore like to present it with some hesitation as the diagnosis.

DR ALFRED KRANES: Would Dr Short care to comment on the possibility of acute bacterial endocarditis? Having just missed a case at one of these conferences I bring it up for his consideration.

DR SHORT: We have a patient who died with fever. We have no other positive evidence, have we?

DR KRANES: No, except that attention is drawn toward the heart, and there was a questionably enlarged spleen. I do not see how one can establish the diagnosis, but perhaps one should consider it as a possibility.

DR SHORT: Yes, I should have mentioned it as a possibility. I agree that there is not enough evidence to make the diagnosis, however.

DR CONGER WILLIAMS: It should be emphasized that those who took care of this patient were limited to the objective findings. The history was entirely worthless because of language difficulty. We thought at first that the history did not suggest myocardial infarction. Later, on learning the electrocardiographic findings, we inclined more

toward that diagnosis. We did consider pericarditis but thought that myocardial infarction was more probable.

#### CLINICAL DIAGNOSES

Myocardial infarction  
Congestive heart failure  
Diabetes mellitus

#### DR SHORT'S DIAGNOSES

Purulent pericarditis  
Coronary heart disease

#### ANATOMICAL DIAGNOSES

*Abscesses, myocardial, left ventricle*  
Pericarditis, fibrinopurulent, acute  
(Diabetes mellitus)  
Hydrothorax, bilateral, moderate  
Pulmonary atelectasis, lower lobes, bilateral  
Cirrhosis of liver  
Rheumatic heart disease  
Endocarditis, chronic, rheumatic, mitral valve, slight  
Arteriosclerosis, generalized, severe, with ulcerations in aorta  
Intercapillary glomerulosclerosis

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Autopsy showed a serofibrinous pericarditis and a greatly hypertrophied heart. On cutting into the heart we found a large abscess of the myocardium, and microscopically many smaller abscesses were observed throughout the myocardium. I think that the pericarditis was unquestionably secondary to the myocardial abscesses. The coronary arteries were markedly sclerotic, but none were occluded. The lungs showed only severe passive congestion—no pneumonia or infarction. Nowhere in the body did we find any other septic focus, there were no other abscesses to which this myocardial abscess might have been secondary.

There was a severe degree of cirrhosis of the liver of a rather nonspecific type that I could not classify. The organ was quite granular grossly, distinctly tougher than normal, and fat infiltration was present in some areas and absent in others. The spleen was hypertrophied, weighing 500 gm, and was fibrotic, indicating that there had been some significant degree of portal hypertension. The kidneys were slightly large, weighing 400 gm, and showed early changes of the type described by Kimmelstiel and Wilson<sup>1</sup>—intercapillary glomerulosclerosis. I doubt if the process had become sufficiently extensive to have had much to do with the symptomatology.

DR ALLAN M. BUTLER: What did the culture show?

DR MALLORY: A culture of the pericardium showed *Staphylococcus aureus*. In a survey of ab-

accases of the myocardium in about 30 cases, reported by Weiss and Wilkins<sup>2</sup> some years ago, 80 per cent were due to the staphylococcus and the remainder to a scattering of other organisms.

DR BUTLER The post-mortem blood culture showed no growth?

DR MALLORY Cocci were present, and other organisms as well, there was undoubtedly a contamination.

DR SHORT Was there actual rupture into the pericardium, or was it involved merely by extension?

DR MALLORY Merely by extension.

A PHYSICIAN Did the marked arteriosclerosis of the aorta have anything to do with it?

DR MALLORY There was marked sclerosis present. I cannot see any way in which it could have contributed to the symptoms.

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#### CASE 33412

##### PRESENTATION OF CASE

A fifty-two-year-old unmarried typist was referred to the Out Patient Department because of persistent cough and nervousness.

She had apparently been in good health until four and a half months before entry, when she noticed swelling and a dull pain in the legs, slight shortness of breath and a mild, persistent cough productive of white, mucoid sputum. She was then admitted to another hospital, where examination revealed hypertension, an enlarged heart, slight dependent edema and enlarged hilar lymph nodes on x-ray study. She was treated with digitalis, Schemm diet, iron and chest radiation, consisting of four doses of 200 r each. The symptoms cleared, but after six weeks there was still no change in the hilar lymph nodes. The patient was then told that she had Hodgkin's disease, whereupon she became disturbed and despondent. Two weeks before entry she noticed lumps on the right side of the neck. By that time she had lost considerable weight — from 160 pounds a year previously and 150 pounds four months previously to 132 pounds on admission.

The patient had had tuberculous cervical adenitis many years previously, and a hysterectomy had been performed for fibroids seven years before admission. Since then she had been subject to menopausal flashes.

Physical examination revealed a thin, nervous and anxious woman. The fundi showed only slight arteriovenous compression. In the neck there was scarring and induration under the right mandible. There were three hard supraclavicular nodules, 0.5 cm in diameter, on the right and smaller, soft, palpable, anterior cervical lymph nodes. The lungs

were normal. The heart was slightly enlarged, the border of cardiac dullness extending to the left. There was slight pitting edema, especially of the left ankle, associated with many telangiectases. Abdominal, pelvic and neurologic examinations were negative.

The temperature was 99°F, the pulse 80, and the respirations 20. The blood pressure was 215 systolic, 115 diastolic.

Examination of the blood disclosed a red-cell count of 4,380,000, with a hemoglobin of 13.8 gm, and a white-cell count of 8200, with 55 per cent neutrophils, 2 per cent large lymphocytes, 25 per cent small lymphocytes, 12 per cent monocytes, 4 per cent eosinophils and 2 per cent basophils. The total serum protein was 6.90 gm per 100 cc, with 4.7 gm of albumin and 2.2 gm of globulin (albumin-globulin ratio of 2.1). The urine was normal. A guaiac test of the stool was negative, as was a blood Hinton test.

An x-ray film of the chest (Fig. 1) showed thickened lung roots and swelling of the right paratracheal lymph nodes. The lung markings were increased, and the left leaf of the diaphragm was obscured. The spleen was not enlarged.

A biopsy of a cervical lymph node was done.

##### DIFFERENTIAL DIAGNOSIS

DR WILLIAM MCK JEFFRIES May we see the x-ray films?

DR STANLEY M WYMAN These films show rather symmetrical enlargement of the lymph nodes at both hili, and there is apparently one large node in the right paratracheal region. The vascular shadows in both lung fields are diffusely prominent, and in the left lower-lung field there is some mottled infiltration, partially obscuring the diaphragm and apparently lying in the lower lobe. The heart shadow is slightly increased in size, enlargement being chiefly toward the left, possibly owing to left ventricular enlargement.

DR JEFFRIES The chief problem presented in this case is one of the differential diagnosis of the causes of enlargement of the mediastinal lymph nodes in a woman of fifty-two years. There are very few positive findings in the history, physical examination or laboratory studies that give a clue to the nature of the process.

The patient had noticed no symptoms until four and a half months before entry, at which time dyspnea, leg edema and a persistent productive cough developed. At another hospital she was found to have hypertension and an enlarged heart, as well as enlarged hilar lymph nodes, and after treatment with digitalis, iron and 800 r of x-ray therapy, the symptoms cleared without evident change in the size of the nodes, suggesting that the edema and dyspnea were due to hypertensive heart disease with failure. The cough apparently recurred, however, since we are told that it was a presenting com-

plaint at the time of admission to this hospital. When the lymph nodes failed to respond to x-ray treatment, the patient was told that she had Hodgkin's disease, but apparently no biopsy was taken — probably because no suspicious superficial lymph nodes had presented themselves at that time. Two weeks before entry here, however, lumps appeared in the right supraclavicular area. In the meantime she had lost 28 pounds during the previous year, 18 of which had been lost in the four months prior to entry. Some of this weight loss may have resulted from digitalization. We are not given any information regarding her appetite, but we are told that she

tion of the supraclavicular and cervical lymph nodes is compatible, since Hodgkin's nodes are usually rather discrete and may vary greatly in texture. The blood studies are not particularly helpful. This patient had comparatively normal red-cell and white cell counts, with a slight increase of monocytes on the differential smear. Although patients with Hodgkin's disease most frequently show a normochromic or hypochromic anemia, with a moderate leukocytosis and an increase in the polymorphonuclear neutrophils, normal counts are not unusual. The eosinophil count of 4 per cent is at the upper limits of normal, but it is now realized that eosinophilia is not so common in Hodgkin's disease as it was formerly thought to be.

The history of failure of the mediastinal lymph nodes to respond to x-ray treatment is somewhat against Hodgkin's disease, although some radiologists report that a dosage of over 1000 r is necessary to cause decrease in size of some mediastinal lesions of this disease. The remarkably symmetrical enlargement of the hilar lymph nodes is also apparently unusual in Hodgkin's disease, so that it might be worth while to consider other possibilities in this case.

Other types of lymphoma should be considered, but here also the lack of radiosensitivity makes this diagnosis rather unlikely.

Could this have been tuberculosis? The history of tuberculous cervical adenitis many years previously is suggestive, but the paucity of clinical signs and the appearance of the mediastinal nodes on x-ray examination are unusual for this disease. Tuberculous mediastinal lymph nodes would not ordinarily be so large or so symmetrically distributed as those in this case.

Bronchiogenic carcinoma can likewise probably be dismissed on the basis of the x-ray picture of symmetrically enlarged hilar lymph nodes.

There is a condition, however, in which such symmetrical enlargement of the hilar nodes, accompanied by enlargement of the paratracheal nodes, and varying degrees of peripheral lymphadenopathy are described as characteristic — that is, Boeck's sarcoidosis.<sup>1</sup> It seems to occur most frequently in younger persons, the greatest incidence being in the third decade, but cases have been reported in patients up to seventy-four years old. The sex incidence is fairly equally distributed between males and females. A characteristic x-ray finding in addition to the striking enlargement of the mediastinal lymph nodes is pulmonary infiltration with linear or nodular densities.<sup>2</sup> There are few or no clinical symptoms, although the occurrence of cough has been reported in a few cases. It is remarkable that even in the presence of greatly enlarged hilar and paratracheal lymph nodes, there is usually no evidence of compression of the trachea or bronchial tree. So far as I know these nodes are not radiosensitive. The blood picture is not characteristic

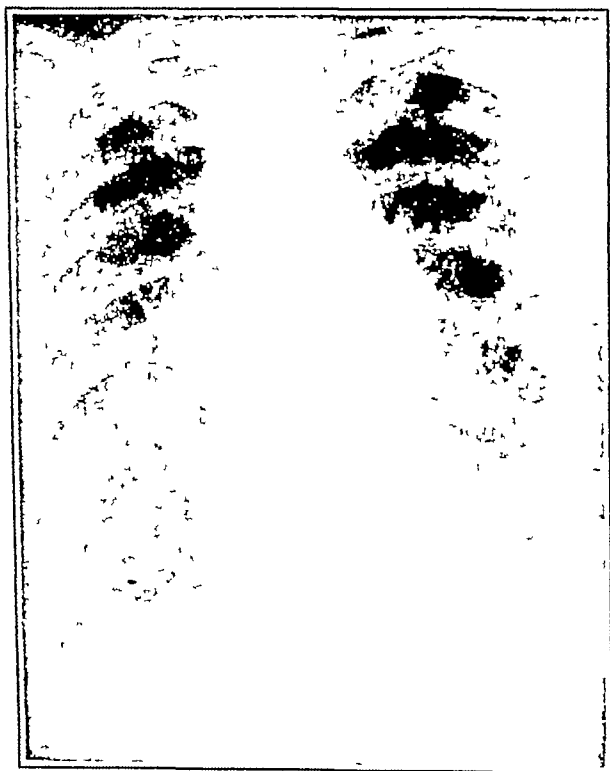


FIGURE 1

had become disturbed and despondent after hearing that she had Hodgkin's disease, so that a good part of the weight loss may have been due to emotional disturbance rather than to the underlying disease.

We are therefore obliged to explain the cause of the enlargement of the mediastinal, right supraclavicular and anterior cervical lymph nodes, associated with productive cough of four and a half months' duration and weight loss, which may or may not have been related.

Could this patient have had Hodgkin's disease? That is certainly one of the most frequent causes of enlargement of mediastinal and cervical lymph nodes. It can occur at any age. Although it is somewhat more frequent in males, 30 to 40 per cent of reported cases have been in females. The descrip-

but the white-cell count is usually normal or low, and an increase in monocytes, with an otherwise normal differential, has been noted in some cases. An eosinophil count of up to 35 per cent has been reported in about a third of the cases. A striking feature found in many cases of sarcoidosis but not observed in this case is an elevation of the plasma globulin, the albumin and globulin were within normal range in the case under discussion. Characteristic areas of cyst-like rarefaction in the bones of the hands and feet have also been reported in approximately 10 per cent of cases in this country, but no mention is made of x-ray studies of the hands or feet in this case.

DR WYMAN X-ray films of the hands and feet were taken but showed no abnormality.

DR JEFFRIES That indicates that sarcoidosis was also suspected. Uveoparotid fever has also been reported in over a third of cases of this disease but was not present in this case.

The weight loss is unusual for sarcoidosis, but some loss of weight has been reported in a few cases and as I have already mentioned, this patient may have lost weight because of emotional disturbance or digitalization.

Finally, two other conditions that may cause chest x-ray findings of this nature should be mentioned. Coccidioidomycosis, or San Joaquin Valley fever is one, but the clinical course is similar to that of influenza or primary atypical pneumonia, chest pain being a prominent feature, and the white-cell count is usually elevated. Patients with this condition usually give a history of having visited or lived in the endemic areas of southwestern United States. The other is erythema nodosum, but in the absence of the classic skin lesions of this condition one could hardly make the diagnosis. It has been suggested by some that erythema nodosum is related to sarcoidosis, and erythema nodosum has also been reported in cases of coccidioidomycosis, so that

the similarity of mediastinal x-ray findings may be more than coincidental.<sup>3</sup>

Therefore, we are left with two chief possibilities: Hodgkin's disease and sarcoidosis, and on the basis of the clinical picture, the x-ray findings and the resistance to x-ray treatment, sarcoidosis seems to have been slightly more probable.

#### CLINICAL DIAGNOSIS

Sarcoidosis?

Hodgkin's disease?

#### DR JEFFRIES'S DIAGNOSIS

Sarcoidosis

#### ANATOMICAL DIAGNOSIS

Sarcoidosis

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN Biopsy of the cervical lymph node showed the characteristic microscopical findings of sarcoidosis. The node was almost completely replaced by well formed groups of epithelioid cells in good tubercle formation. Langhans giant cells were present in moderate numbers. In a few places there were small areas of necrosis, but this finding does not mean tuberculosis. We have seen foci of necrosis in well established cases of sarcoidosis. It would be interesting to have had a tuberculin test, in the majority of cases with sarcoidosis, the tuberculin test is negative.

A PHYSICIAN When the patient was seen in the Out Patient Department three months after the biopsy, no change was noted in her condition.

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## GREATER BOSTON COMMUNITY FUND

PHYSICIANS are well aware of the need for the different kinds of service that more than three hundred Red Feather agencies of the Greater Boston Community Fund give to the people of this close-knit area of fifty cities and towns. Undoubtedly, they are familiar with the medical services offered, in which most of them probably take an active part. The medical profession is so close to the medical aspects, however, that the other valuable services to the community that the Red Feather symbolizes may be overlooked.

Of each dollar contributed last year, youth agencies and neighborhood houses received the largest share — 30 cents — for wholesome recreation for 290,562 people of all ages. Hospitals and dispen-

saries, which received 28 cents of the dollar, provided free or partly free care and 719,897 examinations and treatments for 28,435 patients. Next in line were family services, which received 19 cents of the dollar and which helped 20,773 families in time of trouble. Child-caring agencies — allotted 10 cents of the Red Feather dollar — gave 347,180 days of motherly care in foster homes to neglected children and 35,956 days to small children in day nurseries and nursery schools. Of the remainder of the dollar, 5 cents went to visiting-nurse care, 4 cents for the handicapped and aged, and 4 cents for fifty-four diversified special services.

Physicians affiliated with Red Feather hospitals may regard some of the services that they contribute as fulfilling the demands that the community makes on them. Money, however, is also needed to help meet operational expenses of all the Red Feather agencies, struggling against mounting costs in every field. It is well to remember that, whereas two out of five families in Greater Boston receive direct help from Red Feather services, everyone benefits in some way from the protection that these health and social agencies give to the community.

In the aftermath of war, the needs have increased — the old ones have been accentuated, and many new ones have developed. Family life has been disrupted and broken. Health and nerves have been taxed to the danger point. There is confusion and relaxation of normal standards. Young people are restless and undisciplined. Family and child welfare agencies probably bear the brunt of these increased needs as they face the situations caused by breaking of homes during the war, the soaring figures on illegitimacy, the unhappy young couples who married too hastily and the tremendous upsurge of juvenile delinquency.

Remembering that there are many needs beyond the call of medical duty, physicians should do their utmost to enable the Red Feather services to carry on in 1948.

## SULFADIAZINE-RESISTANT STREPTOCOCCAL INFECTIONS AMONG CIVILIANS

AT THE height of the war, certain personnel of the armed services participated in a program of continuous prophylaxis with daily small doses of sulfa-

diazine in an attempt to minimize the number of man-days lost through streptococcal illness, particularly during the crucial initial training period. Among the possible complications that were expected to arise out of this program were the development and spread of sulfonamide-resistant strains of bacteria. The occurrence of such resistant organisms in military units was subsequently reported, and because of this the chemoprophylactic program was abandoned.

The mode of development of the resistant strains of bacteria has not been settled. It has been shown that strains of streptococci with slight degrees of sulfadiazine resistance appeared among Army personnel about the time when the program of mass chemoprophylaxis had already been in progress in the Navy for several months. It is possible that these slightly resistant strains were the precursors of the more highly resistant ones that later became established. It is also possible that resistant strains were transferred from certain Navy personnel who had been subjected to the prophylactic program and might have become carriers of the highly resistant streptococci. Interestingly enough there was no evidence of the existence of sulfonamide-resistant strains of hemolytic streptococci prior to the institution of the mass chemoprophylactic program.

The evidence to date seems to indicate that all strains of hemolytic streptococci that were present in the civilian population prior to the time of mass chemoprophylaxis in the armed forces were susceptible to the action of sulfonamides. Furthermore, there is some evidence to show that the therapeutic doses of sulfonamides, as usually prescribed among civilians, do not cause the development of resistant organisms.

Since large numbers of personnel in the armed services were exposed to sulfonamide-resistant strains and since there were many opportunities for mingling of service personnel with civilians, it could be anticipated that sooner or later the resistant streptococci would be found among civilians. The occurrence of an outbreak of streptococcal infections due to a resistant strain has now been reported among civilians in a small community by Johnson and Hartman\*.

Early in 1946 an epidemic of scarlet fever occurred in Cooperstown, New York. The first 8 patients that were studied were found to harbor Type 19 hemolytic streptococci. This was one of the types that had been found to account for a large proportion of the sulfonamide-resistant streptococci that spread among military personnel. It was decided, therefore, to determine whether the strains from this outbreak were sulfonamide-resistant. All eight strains were found to be resistant to sodium sulfadiazine in a concentration of 25 mg per 100 cc.

This offered a unique opportunity to study the incidence of sulfonamide-resistant hemolytic streptococci in a small community. Cultures were obtained from patients living in Cooperstown and in the surrounding area of Otsego County who were suspected of having streptococcal infections. Strains from 100 patients were collected between the middle of February and the end of April, 1946. Two specific types were found to predominate: Type 3, which accounted for twenty-eight strains, and Type 19, which accounted for twenty-four strains. The remaining strains were of other specific types or could not be typed with the available diagnostic serums. All but one of the Type 19 strains were found to be sulfadiazine-resistant, whereas none of the remaining strains were resistant.

Of the cases of drug-resistant infection, 14 were clinical scarlet fever, and 9 were simple pharyngitis; 9 cases occurred in adults, and the rest were in children of school age or younger. The first case of scarlet fever occurred in a boy who was attending public school, following the onset of his illness, several of his classmates developed scarlet fever, and Type 19 sulfadiazine-resistant streptococci were isolated from all. The same organism was isolated from the parents, siblings and contacts of children originally infected in this public school. There were 3 patients, however, who had had no contact with any of these patients, nor had they had any known contact with recently discharged or active members of the armed services.

It is stated that these cases offered no particular therapeutic difficulties. It is not mentioned, however, whether any specific antibacterial agent, particularly sulfadiazine, was used. Obviously, if these cases were mild and if penicillin were used, no cases would be expected.

\*Johnson R. D., and Hartman T. L. Sulfadiazine resistant streptococcal infections in civilian community. *J. Clin. Investigation* 26:325, 328, 1947.



The development of resistance to antibacterial agents has become particularly important since the introduction of streptomycin. The emergence of streptomycin-resistant strains during treatment has been one of the most important factors limiting the successful use of that antibiotic. Drug-fastness, moreover, is the most important factor limiting the usefulness of the sulfonamides in the treatment of gonococcal infections. Fortunately, penicillin has been highly effective against infections with sulfonamide-resistant strains of gonococci. Furthermore, the widespread use of penicillin has thus far failed to give rise to penicillin-resistant strains to any significant extent. Whether attempts to use penicillin prophylactically on a wide scale or over a long period would result in the emergence of penicillin-resistant strains remains problematic.

In the meantime it is important to be on the lookout for the appearance and spread of pathogenic bacteria resistant to the chemotherapeutic and antibiotic agents, particularly in patients in whom the results of therapy with such agents are disappointing.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

**BROWN** — Martin M. Brown, M.D., of North Adams, died on September 18. He was in his eighty-fifth year.

Dr. Brown received his degree from Rush Medical College in 1888. He had practiced medicine and surgery in North Adams for fifty-six years. He was a fellow of the American College of Surgeons and the American Medical Association.

**CHARRON** — Ovide Toussaint Charron, M.D., of New Bedford, died on May 26. He was in his sixty-fifth year.

Dr. Charron received his degree from College of Physicians and Surgeons, Boston, in 1912. He was a former member of the Massachusetts Medical Society.

**COWLES** — Frank Augustus Cowles, M.D., of Beverly, died on May 21. He was in his eighty-eighth year.

Dr. Cowles received his degree from University of the City of New York Medical Department in 1881. He was a former member of the Massachusetts Medical Society.

**HIGGINS** — George V. Higgins, M.D., of Randolph, died on September 8. He was in his sixty-seventh year.

Dr. Higgins received his degree from Tufts College Medical School in 1906. He was a former president of the Norfolk South District Medical Society and for thirty-five years was associate medical examiner for Norfolk County. He was a fellow of the American Medical Association.

His widow and three brothers survive.

**JOHNSON** — Mary W. L. Johnson, M.D., of Boston, died on September 15. She was in her eighty-first year.

Dr. Johnson received her degree from Women's Medical College of Pennsylvania in 1894. From 1905 to 1912 she was assistant superintendent of Inwood Sanitarium, Conshohocken, Pennsylvania, and in 1914 she founded Bellevue Hospital in Chestnut Hill.

A daughter and two nephews survive.

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- TRUMBULL, MERLIN L. Beverly Hospital, Beverly  
University of Nebraska College of Medicine 1940.
- WEISMAN, BERNARD 62 Ocean Street, Lynn.  
College of Physicians and Surgeons, Boston 1940. Sponsor  
Morris Reingold, 15 New Ocean Street Lynn.
- WHITE, NORMAN W. Homestead Road Lynnfield Center  
Jefferson Medical College of Philadelphia, 1930  
Henry D. Stebbins *Secretary*  
342 Essex Street Salem

## FRANKLIN DISTRICT

- DODD, WILSON F., Mount Hermon.  
Cornell University Medical College 1920
- ELOSOM, EMID D., 26 Bridge Street Millers Falls.  
McGill University Faculty of Medicine, 1940  
Harry L. Craft, *Secretary*  
Ashfield

## HAMPTON DISTRICT

- BERNSTEIN, JOSEPH I., 127 Jefferson Avenue, Springfield  
Middlesex University School of Medicine 1942 Sponsor  
Aurel G. Lavoie, 14 Chestnut Street, Springfield
- BLOOM, BERNARD 67 Chestnut Street, Springfield  
New York University College of Medicine 1938
- BURKE, JOHN A. 337 Appleton Street, Holyoke  
Tufts College Medical School 1940
- CONWAY, RAYMOND F., 2068 Northampton Street, Holyoke.  
Boston University School of Medicine, 1941
- EGAN, DONALD F. 293 Bridge Street, Springfield.  
Tufts College Medical School, 1943
- HALTON, EDWARD J., 337 Appleton Street, Holyoke  
Jefferson Medical College of Philadelphia, 1938.
- HERBERT, ROGER D., 44 Chestnut Street, Springfield  
Laval University Faculty of Medicine, 1939
- JORDAN, FRANK J., JR. 34 Maple Street Springfield  
Tufts College Medical School, 1940
- KEITLEN, PHILIP B., 95 State Street, Springfield.  
Eclectic Medical College 1939 Sponsor Alfred Glickman  
283 Longhill Street, Springfield.
- NEWMAN, WALTER, 115 State Street, Springfield  
University of Graz, Austria 1923 Sponsor Max Millman  
111 Maple Street, Springfield
- PENDOLA, JOSEPH J., 80 Beacon Street, Boston.  
Hahnemann Medical College and Hospital of Philadelphia  
1940.
- POTSUBAT, SAMUEL F. 323 Appleton Street, Holyoke  
Harvard Medical School 1940
- TAUBER, JOSEPH 820 State Street Springfield  
University of Vienna 1921 Sponsor Alfred Hollander  
458 Bridge Street, Springfield.
- VASH, GEORGE, Main Street, Chester  
University of Vienna 1937 Sponsor Archibald J. Douglas  
Westfield
- ZIELINSKI, JOSEPH F., 337 Appleton Street Holyoke  
Jefferson Medical College of Philadelphia, 1938.  
George C. Steele, *Secretary*  
39 Upper Church Street West Springfield

## HAMPSHIRE DISTRICT

- CAVANAUGH, JAMES E. Cooley Dickinson Hospital  
Northampton  
Dartmouth Medical School 1936.
- DIETEL, ROBERT C., 48 Bardwell Street South Hadley Falls  
Jefferson Medical College of Philadelphia, 1946.

HORGAN, JOHN D., Cummington  
New York Medical College, 1945

MICHIEWICZ, MATTHEW S., 25 Main Street, Northampton  
New York Medical College, 1941

WINSTEN, SOL S., Veterans Administration Hospital,  
Northampton  
University of Berne, Switzerland, 1939 Sponsor Benjamin  
G. Morrison, Veterans Administration Hospital, Northamp-  
ton

F. Mary P. Snook, *Secretary*  
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#### MIDDLESEX EAST DISTRICT

CODIN, KENNETH, 28 High Street, Stoneham  
Middlesex University School of Medicine, 1941 Sponsor  
C. R. Hardcastle, 55 Elm Street, Woburn

FOLDES, FRANCIS F., 8 Fenwick Road, Melrose  
University of Budapest, 1934 Sponsor Jost J. Michelsen,  
311 Beacon Street, Boston

LEAVITT, HENRY E., 26 Maple Street, Stoneham  
Middlesex University School of Medicine, 1938 Sponsor  
Howard A. Bouvé, 520 Commonwealth Avenue, Boston

LEVINE, SIDNEY A., 5 Faulkner Place, Melrose  
George Washington University School of Medicine, 1941

MCCARTHY, FRANCIS D., 229 Main Street, Melrose  
Tufts College Medical School, 1944

MCLEAN, DONALD E., 81 Bacon Street, Winchester  
Harvard Medical School, 1943

ORR, ROBERT B., 64 Westland Avenue, Winchester  
University of Virginia Department of Medicine, 1938

REID, DAVID H., 274 Porter Street, Melrose  
Tufts College Medical School, 1943

SOULE, ROBERT M., 8 Porter Street, Melrose  
Harvard Medical School, 1943

SZDLOWSKI, SIGMUND J., 12 Richardson Avenue, Wakefield  
Middlesex University School of Medicine, 1941 Sponsor  
Howard A. Bouvé, 520 Commonwealth Avenue, Boston

WEST, GEORGE V., 22 Irving Street, Reading  
Tufts College Medical School, 1944

YOUNG, JACK G., 7 Tremont Street, Stoneham  
Baylor University College of Medicine, 1940

Roy W. Layton, *Secretary*  
8 Porter Street, Melrose

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BARRY, JOHN J., 27 Milard Avenue, Chelmsford  
Middlesex University School of Medicine, 1941 Sponsor  
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BEER, ERNEST G., 66 Victoria Street, Lowell  
University of Heidelberg, 1923 Sponsor Archibald R.  
Gardner, 16 Shattuck Street, Lowell

BLUMENTHAL, IRVING J., Veterans Administration Hospital,  
Bedford  
University of Freiburg, 1937 Sponsor Aaron H. Braver-  
man, Veterans Administration Hospital, Bedford

GRAINGER, HENRY B., Tewksbury State Hospital, Tewks-  
bury  
Tufts College Medical School, 1943

MEISLIN, JACOB, Veterans Administration Hospital, Bedford  
University of Lausanne, 1936 Sponsor Morris Zellin,  
Veterans Administration Hospital, Bedford

Brendan D. Leahy, *Secretary*  
9 Central Street, Lowell

#### MIDDLESEX SOUTH DISTRICT

ABBOTT, RICHARD N., 6 Crocker Circle, West Newton  
Yale University School of Medicine, 1943

APPEL, CHARLES F., 330 Mt. Auburn Street, Cambridge  
Jefferson Medical College of Philadelphia, 1941

ARMSTRONG, BEVERLY W., 135 Washington Street, Brighton  
Syracuse University College of Medicine, 1941

AVOLA, FRANCIS A., 17 Dwyer Circle, Medford  
Tufts College Medical School, 1944

BARGER, A. CLIFFORD, 65 Strathmore Road, Brighton.  
Harvard Medical School, 1943

BASKIES, BARNET, 380 Salem Street, Medford  
College of Physicians and Surgeons, Medical Department,  
Kansas City University, 1938 Sponsor Henry M. Galt,  
19 Washington Street, Medford

CROISSANT, EDWARD D., 371 Belmont Street, Belmont.  
Middlesex University School of Medicine, 1940 Sponsor  
Max Ritvo, 416 Marlboro Street, Boston

DEXTER, CHESTER J., 1 Chiswick Terrace, Brighton  
Harvard Medical School, 1943

DOMENICI, TRENTO J., 83 Bowdoin Street, Medford  
Marquette University School of Medicine, 1942

DONOVAN, ROBERT E., 45 Hopkins Road, Arlington  
Middlesex University School of Medicine, 1940 Sponsor  
Fred R. Jouett, 1 Craigie Street, Cambridge.

ETTENBERG, MAX, 120 White Street, Belmont.  
Middlesex University School of Medicine, 1940 Sponsor  
Jacob L. Rudd, 57 Lee Street, Cambridge

GATES, PHILIP H., 4 Walnut Avenue, Cambridge  
University of Minnesota Medical School, 1937

GORFINE, MORRIS, 897 Massachusetts Avenue, Cambridge.  
Middlesex University School of Medicine, 1938 Sponsor  
Jacob N. Newman, 140 Prospect Street, Cambridge.

GUENTHER, RICHARD A., 7 Revere Place, Medford  
Tufts College Medical School, 1943

HESTER, JAMES W., 115 Mt. Auburn Street, Cambridge.  
Tufts College Medical School, 1941

INSERRA, FRANK, 336 High Street, Medford  
Tufts College Medical School, 1941

JOSEPH, ALFRED T., 4 Shaler Lane, Cambridge  
Tufts College Medical School, 1943

KAUFMAN, I. CHARLES, 215 Islington Road, Auburndale.  
Long Island College of Medicine, 1943

KROGER, LOUIS E., 90 Nonantum Street, Brighton  
University of Cincinnati College of Medicine, 1935

KRUSH, THADDEUS P., 289 Park Street, Newton  
Western Reserve University School of Medicine, 1941

KUBIN, LUDWIG, 19 Appleton Street, Waltham  
University of Vienna, 1920 Sponsor Nathaniel P.  
Brackett, 826 Main Street, Waltham

LAZANSKY, JOSEPH P., 14 Skahan Road, Belmont.  
University of Prague, 1923 Sponsor Ralph E. Wheeler,  
416 Huntington Avenue, Boston.

LICHT, SIDNEY, 30 Hillside Avenue, Cambridge  
New York University College of Medicine, 1931

LUCACER, MICHAEL, 1488 Cambridge Street, Cambridge.  
Royal University of Palermo, 1926 Sponsor Myer Marlin,  
385 Broadway, Cambridge

LYNCH, JOSEPH P., JR., 69 Tremont Street, Marlboro  
Boston University School of Medicine, 1943

MACKENZIE, MICHAEL V., 20 Dutton Circle, Medford  
Tufts College Medical School, 1938

NELSON, ROBERT E., 63 Chester Street, Arlington  
University of Oregon Medical School, 1937

NEWCOMBE, RICHARD V., 8 Berkley Street, Arlington Heights  
University of Vermont College of Medicine, 1940

NEWERLA, GERHARD J., 112 Vernon Street, Waltham  
Middlesex University School of Medicine, 1942 Sponsor  
H. Quimby Gallupe, 751 Main Street, Waltham

PICARIELLO, AMERICO, 104 Holland Street, Somerville.  
Middlesex University School of Medicine, 1937 Sponsor  
Anthony Russo, 2 Austin Street, Somerville

PIOUS, LAWRENCE K., 255 Bedford Street, Lexington  
Middlesex University School of Medicine, 1940 Sponsor  
Winthrop Harrington, 1900 Massachusetts Avenue, Lex-  
ington

QUINN, EDMUND P., 153 Middlesex Avenue, Medford  
Tufts College Medical School, 1943

RAPHAEL, SUMNER I., 15 Greycliff Road, Brighton  
Tufts College Medical School, 1943

RILEY, LEO H., JR., 173 Jackson Road, Newton  
Boston University School of Medicine, 1943

- OSKRAUM, JACK D., 35 Winter Street, Framingham Centre  
Yale University School of Medicine, 1937
- PAPIENZA, PETER L., 683 Broadway, Everett.  
Boston University School of Medicine, 1943
- PERKINS, FRANCIS W., 384 Broadway Cambridge.  
Tufts College Medical School, 1943
- RYDER, FRANKLIN F., 216 Arnold Road Newton Centre  
Johns Hopkins University School of Medicine, 1923
- SOULIOTS, PAUL T., 330 Mt. Auburn Street, Cambridge.  
Hahnemann Medical College of Philadelphia, 1940.
- TEDESCHI, C. George, Singletary Lane, Framingham  
University of Bologna, 1929 Sponsor Joseph C. Meriam,  
198 Union Avenue, Framingham
- TIMBERLAKE, WILLIAM H., 10 Appian Way, Cambridge  
Tufts College Medical School 1943
- TROUBALOS, STEPHEN, 55 Brock Street, Brighton.  
Marquette University School of Medicine, 1943
- WEINER, Joseph 523 Ward Street, Newton Centre  
Vanderbilt University School of Medicine, 1935
- Alexander A. Levi, *Secretary*  
481 Beacon Street, Boston

NORFOLK DISTRICT

- ABRAMS ARTHUR L., 9 Gibbs Street, Brookline.  
Harvard Medical School, 1938
- BALLANTINE, HENRY T., JR., 180 Clyde Street, Brookline  
Johns Hopkins University School of Medicine, 1937
- BREAN HENRY P., Peter Bent Brigham Hospital, Boston  
Harvard Medical School, 1943
- BREITWISER EDNA R. Wellesley College Wellesley  
University of Pennsylvania School of Medicine, 1943
- BRUNNER-ORNE, MARTHA, 117 Winter Street, Westwood  
University of Vienna 1920. Sponsor Sidney M Bunker  
Westwood Lodge, Westwood
- BURBAK, CHARLES B. 43 Sumner Road Brookline  
Harvard Medical School, 1938
- COHEN MILTON 132 Columbia Street Brookline.  
Tufts College Medical School 1939
- COLEMAN NATHAN W. 235 Reeddale Road, Milton  
Middlesex University School of Medicine, 1941 Sponsor  
Eli Friedman 416 Marlborough Street, Boston.
- CONDON ROBERT V. 44 Westbourne Street, Roslindale  
Tufts College Medical School, 1940
- DENTON WILLIAM I. 33 Wall Street Wellesley  
University of Rochester School of Medicine, 1942.
- DRAKE, EMERSON H., 935 High Street, Dedham  
Columbia University College of Physicians and Surgeons  
1941
- DRAKE, WILLIAM L. JR., 20 Netherlands Road Brookline  
Marquette University School of Medicine 1943
- EMERSON CHARLES P., JR., 29 Sheridan Road Wellesley Hills.  
Harvard Medical School 1937
- FOLEY JOSEPH M., 19 Willis Street Dorchester  
Harvard Medical School, 1941
- GOLDSTEIN ROBERT, 44 Stearns Road Brookline  
Harvard Medical School 1937
- GRAY, WILLIAM 166 Thorndike Street, Brookline  
University of Nebraska College of Medicine, 1941
- HARWOOD PAUL H. JR., 240 South Street, Chestnut Hill  
Harvard Medical School, 1939
- HAYEK, AUGUSTA 85 Naples Road Brookline.  
University of Vienna 1921 Sponsor Blanche L. Atwood  
29 Powell Street, Brookline
- HOMANS, JOHN JR., 33 Leicester Street, Brookline.  
Harvard Medical School 1941
- KARRAS JOSEPH D. 82 Stedman Street, Brookline  
Middlesex University School of Medicine, 1937 Sponsor  
Leon Rosenfeld, 371 Commonwealth Avenue Boston
- KOENIG ARTHUR T. JR., 41 Clifmont Street, Roslindale  
New York Medical College 1943
- LARIM, JOHN J., 215 Perham Street, West Roxbury  
Harvard Medical School 1939
- LIFT, PHILIP A. 29 Brookledge Street, Roxbury  
New York University College of Medicine 1941

- LYMAN, LEWIS 152 Neponset Avenue, Dorchester  
College of Physicians and Surgeons, Boston, 1937 Sponsor  
Norman A. Welch 520 Commonwealth Avenue, Boston
- MAISON, GEORGE L. 310 Harris Avenue Needham  
Northwestern University Medical School, 1935
- MASSIE, PAUL, 18 Alpha Road Dorchester  
Tufts College Medical School, 1942
- MEZINE, DAVID I., 2089 Centre Street, West Roxbury  
Middlesex University School of Medicine, 1937 Sponsor  
Samuel N. Marney, 311 Commonwealth Avenue, Boston
- MILLER, HYMAN 999 Dorchester Avenue, Dorchester  
Middlesex University School of Medicine, 1930 Sponsor  
Humphrey L. McCarthy, 479 Beacon Street, Boston
- MONAHAN JOHN L., 2 Laban Pratt Road, Dorchester  
Tufts College Medical School 1943
- MULLIGAN WILLIAM J. 32 Cumberland Avenue Brookline.  
University of Vermont College of Medicine 1941
- O'HARE, JAMES M. 356 Newton Street, Chestnut Hill  
Harvard Medical School 1945
- POLATIN SYDNEY 4251 Washington Street, Roslindale.  
Middlesex University School of Medicine, 1942. Sponsor  
Henry Baker 453 Beacon Street, Boston.
- RACIOPPI FRANCESCA M. 152 Washington Street, Wellesley  
Hills  
Boston University School of Medicine, 1941
- RIMMER ROBERT W. 62 Winter Street Norwood.  
Tufts College Medical School 1942.
- SCHULTZ, JOHN D. 485 Heath Street, Chestnut Hill.  
Johns Hopkins University School of Medicine, 1937
- SHAUFFER, IRVING A. 4 Lawrence Road, Brookline.  
Tufts College Medical School 1943
- SPELFOGL, BENJAMIN, 20 Duke Street, Mattapan  
Middlesex University School of Medicine, 1941 Sponsor  
Jacob Chayer 1807 Beacon Street, Brookline.
- SPENCE, PHILIP S., 4648 Washington Street, Roslindale.  
Boston University School of Medicine, 1943
- SWEET WILLIAM H. 35 Chestnut Place Brookline.  
Harvard Medical School 1936.
- THOMPSON WILLIAM J. 2076 Washington Street, Canton  
Middlesex University School of Medicine, 1936. Sponsor  
William F. Croaker, 1101 Beacon Street, Brookline
- TRAKAR, JOHN C., 102 Brook Road, Milton.  
Harvard Medical School, 1943
- VAUGHAN ROBERT H., 29 Needham Street, Dedham.  
Harvard Medical School, 1943
- WALDINGER, CLARA 17 Moraine Street, Jamaica Plain.  
University of Vienna 1929 Sponsor Marjorie Woodman,  
21 Bay State Road Boston
- WILSON NORMAN J. 90 Ellicott Street Needham  
University of Maryland School of Medicine 1935
- WIXTED FRANCIS J., 630 Adams Street, East Milton  
Middlesex University School of Medicine 1941 Sponsor:  
John A. Seth 47 Bay State Road Boston
- YATSUBASHI MARAO, Pondville Hospital Walpole  
Harvard Medical School 1944

Basil E. Barton *Secretary*  
10 Richwood Street, West Roxbury

NORFOLK SOUTH DISTRICT

- CLANCY DANIEL H. JR., 100 Washington Street, Weymouth.  
Tufts College Medical School 1943
- CRISMOND LOUIS A. 83 Independence Avenue, Quincy  
George Washington University School of Medicine 1945
- McMARON FRANCIS J. 45 Snell Street Holbrook.  
Boston University School of Medicine, 1942
- MESHOREK, EDWARD 15 Franklin Street, Quincy  
College of Physicians and Surgeons Medical Department,  
Kansas City University 1938. Sponsor Harold R. Record,  
27 Temple Street, Quincy
- NALBAND EDWARD H. 76 Watkins Street Wollaston.  
Tufts College Medical School 1943
- ORRACH RUDI J., 279 Washington Street Quincy  
University of Milan 1934 Sponsor William S. Altman  
32 Spear Street, Quincy

- OSSEN, PAUL I, 208 Merrymount Road, Quincy  
Boston University School of Medicine, 1943
- RUBIN, FRANK F, 795 Southern Artery, Quincy  
Middlesex University School of Medicine, 1937 Sponsor  
Frederick N Manley, 1200 Hancock Street, Quincy
- TROTT, ARTHUR W, 253 Harvard Street, Wollaston  
Harvard Medical School, 1944
- WACKS, JOSEPH S, 76 Franklin Street, South Braintree  
Middlesex University School of Medicine, 1932 Sponsor  
Nathan Zibel, 381 Bridge Street, Weymouth
- WHARTON, CARL M, 56 Sycamore Street, Squantum  
Vanderbilt University School of Medicine, 1940
- WILSON, NORMAN L, 59 Coddington Street, Quincy  
University of Virginia Department of Medicine, 1940

Ebenezer K Jenkins, *Secretary*  
Norfolk County Hospital, South Braintree

#### PLYMOUTH DISTRICT

- ABDU, LOUIS, 64 Provost Street, Brockton  
Tufts College Medical School, 1942.
- BLUMENTHAL, FREDERICK F, 9 Summer Street, Bridgewater  
University of Berlin, 1923 Sponsor Alton L Hurlburt,  
East Bridgewater
- BRITTON, LEE, 31 Clapp Street, Stoughton  
Boston University School of Medicine, 1945
- DONNELLY, JAMES F, 63 Franklin Street, Rockland  
Middlesex University School of Medicine, 1939 Sponsor  
Joseph Dunn, 321 Union Street, Rockland
- GLEASON, CHARLES S, 121 High Street, Warcham  
Tufts College Medical School, 1946
- KAPLAN, MORRIS, Bridgewater State Farm, Bridgewater  
College of Physicians and Surgeons, Boston, 1937 Sponsor  
Abraham L Schwartz, Foxboro State Hospital, Foxboro
- LINGOS, JOHN W, 129 West Elm Street, Brockton  
Middlesex University School of Medicine, 1941 Sponsor  
Ralph C McLeod, 129 West Elm Street, Brockton
- MCENROE, DONALD F, 238 South Avenue, Whitman  
Middlesex University School of Medicine, 1939 Sponsor  
George A Moore, Moore Hospital, Brockton
- MAYO, W VERNON, 119 Summer Street, Kingston  
Middlesex University School of Medicine, 1936 Sponsor  
Harold H Hamilton, 70 Court Street, Plymouth
- PASTER, HAROLD I, 106 Main Street, Brockton  
Middlesex University School of Medicine, 1934 Sponsor  
Michael F Barrett, 231 Main Street, Brockton
- PETRELL, NATALE R, 305 Court Street, North Plymouth  
Middlesex University School of Medicine, 1941 Sponsor  
William E Curtin, 272 Court Street, Plymouth
- THIERY, RAYMOND D, Bridgewater State Farm, Bridgewater  
Harvard Medical School, 1923
- WEIS, SAMUEL, 47 West Elm Street, Brockton  
Tufts College Medical School, 1930
- WHITING, GEORGE L, 317 Washington Street, Abington  
Tufts College Medical School, 1945

Samuel Gale, *Secretary*  
The Checkerton, Brockton

#### SUFFOLK DISTRICT

- CALLOW, ALLAN D, 154 Beach Street, Revere  
Harvard Medical School, 1942
- CANNON, RAYMOND G, 942 East Broadway, South Boston  
Middlesex University School of Medicine, 1940 Sponsor  
John J Todd, 587 Beacon Street, Boston
- DAHL, LEWIS K, Massachusetts General Hospital, Boston  
University of Pennsylvania School of Medicine, 1939
- DEWING, NORMAN F, 868 Beacon Street, Boston  
Middlesex University School of Medicine, 1925 Sponsor  
George P Denny, 101 Bay State Road, Boston
- DIAMOND, ISRAEL, 174 Bay State Road, Boston  
School of Medicine of the Royal Colleges, Edinburgh, 1939  
Sponsor Frank E Barton, 29 Bay State Road, Boston
- DOWNING, WILLIAM M, 195 Pilgrim Road, Boston  
Boston University School of Medicine, 1937

- FERRINO, PETER J, 21 Bennington Street, East Boston.  
College of Physicians and Surgeons, Medical Department  
Kansas City University, 1938 Sponsor G Lynde Gately,  
624 Bennington Street, East Boston
- GREGORIE, JOSEPH, 336 Sumner Street, East Boston.  
Middlesex University School of Medicine, 1941 Sponsor  
Edward J Grainger, 200 Washington Avenue, Winthrop
- GREGORY, IRVING F, 390 Marlborough Street, Boston.  
Tufts College Medical School, 1929
- HUNTRESS, WILLIAM W, 357 Charles Street, Boston  
Tufts College Medical School, 1938
- KENT, CHARLES, 270 Commonwealth Avenue, Boston.  
University of Prague, 1927 Sponsor Philip E Meltzer,  
20 Charlesgate West, Boston
- KURLAND, LEONARD T, 45 Beechcroft Street, Brighton  
University of Maryland School of Medicine, 1945
- LANE, HELEN E, 84 Byron Street, East Boston  
Boston University School of Medicine, 1943
- MEILMAN, EDWARD, 114 Riverway, Boston  
Harvard Medical School, 1940
- MORRIS, JOHN M, 264 Beacon Street, Boston  
Harvard Medical School, 1940
- OGLESBY, PAUL, 81 Pinckney Street, Boston  
Harvard Medical School, 1942
- PERKINS, HERBERT A, Boston City Hospital, Boston.  
Tufts College Medical School, 1943
- PERRY, HELEN S, 97 St. Stephen Street, Boston  
Tufts College Medical School, 1943
- PICK, WALTER, Massachusetts General Hospital, Boston.  
Harvard Medical School, 1942
- ROGERS, JOSEPH, 108 Jersey Street, Boston  
Harvard Medical School, 1941
- ROOPENIAN, ARAM, 716 East Seventh Street, South Boston.  
Tufts College Medical School, 1942.
- ROSENBERG, ISADORE N, 35 Allen Street, Boston.  
Harvard Medical School, 1943
- SCANNELL, JOHN G, Massachusetts General Hospital, Boston.  
Harvard Medical School, 1940
- SPELMAN, PHILIP J, 23 Colonial Road, Providence, Rhode  
Island  
Columbia University College of Physicians and Surgeons,  
1940
- WARNER, FRANK A, 51 Mt. Vernon Street, Boston  
Harvard Medical School, 1935
- WHITNEY, BYRON V, 115 St. Stephen Street, Boston  
Tufts College Medical School, 1944
- WOOL, JACK, Boston City Hospital, Boston  
University of Vermont College of Medicine, 1941
- ZAMCHECK, NORMAN, 25 Shattuck Street, Boston  
Harvard Medical School, 1943

Charles G Shedd, *Secretary*  
422 Beacon Street, Boston

#### WORCESTER DISTRICT

- DOWD, GEORGE C, 216 Main Street, Worcester  
Middlesex University School of Medicine, 1941 Sponsor  
Edward Budnitz, 16 Norwich Street, Worcester
- FLETCHER, MARY E, 10 Institute Road, Worcester  
Syracuse University College of Medicine, 1941
- FOWLER, RICHARD L, 125 Main Street, Spencer  
University of Maryland School of Medicine, 1943
- HADDAD, ALBERT, 18 Wall Street, Worcester  
Albany Medical College, 1943
- HEALY, THOMAS V, 21 Fiske Street, Worcester  
Harvard Medical School, 1943
- HECHLER, ROBERT, Veterans Administration Hospital, Rut  
land Heights  
Columbia University College of Physicians and Surgeons,  
1931
- KAYE, ABRAHAM, Worcester State Hospital, Worcester  
Boston University School of Medicine, 1942.
- MADOFF, IRVING M, 5 Walker Place, Clinton  
New York University College of Medicine, 1943

- LANNING, JOHN J., St. Vincent's Hospital, Worcester  
University of Pennsylvania School of Medicine, 1941
- MARSH, CARL G., 390 Main Street, Worcester  
College of Physicians and Surgeons Medical Department  
Kansas City University, 1942. Sponsor Everett P. Jewett  
390 Main Street, Worcester
- MEHEMAM, BERNARD F. Main Street, Upton  
Middlesex University School of Medicine 1939 Sponsor  
Joseph I. Ashkins 36 Pine Street, Milford
- REAGAN, DANIEL J., 507 Main Street, Worcester  
Harvard Medical School, 1939
- RICHMOND, PAUL, JR., 475 Main Street, Worcester  
Georgetown University School of Medicine 1914
- ROY, JAMES E., 340 Main Street, Worcester  
Harvard Medical School, 1939
- STONE, TIMOTHY P., Southboro  
Tufts College Medical School, 1942
- STREETER, C. CLARKE, Harvard  
Tufts College Medical School 1943
- WHEEL, MILTON H., 91 Elm Street Worcester  
Rush Medical College 1941

Julius J. Tegelsberg *Secretary*  
390 Main Street, Worcester

#### WORCESTER NORTH

- ALEXANDER, DANIEL D. Gardner State Hospital, East  
Gardner  
Middlesex University School of Medicine 1942. Sponsor  
Charles E. Thompson Gardner State Hospital East  
Gardner
- BROWN WESLEY C., Petersham  
College of Physicians and Surgeons Boston 1926 Sponsor  
Donald B. Cheetham 164 Exchange Street, Athol
- DUDIS, ROGER G., 521 Main Street, Athol  
Albany Medical College, 1943
- SILVER, JOSEPH M., 24 Prichard Street, Fitchburg  
Middlesex University School of Medicine, 1942. Sponsor  
John J. Curley, 89 West Street, Leominster
- SPARLING, HAROLD J., JR., 1424 Main Street, Whalom.  
Boston University School of Medicine, 1944
- SPARLING, SEDA A., 1424 Main Street, Whalom  
Boston University School of Medicine, 1944

James G. Simmons *Secretary*  
30 Myrtle Avenue Fitchburg

### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

#### DIAGNOSIS OF UNDULANT FEVER BY LABORATORY TESTS

It is exceedingly difficult to make a diagnosis of undulant fever solely on the basis of clinical data. Among the diseases to be differentiated from it are infectious mononucleosis, tuberculosis, typhoid and similar enteric fevers, syphilis, malaria, subacute bacterial endocarditis, tularemia, Hodgkin's disease and rheumatic fever. In both the acute and the chronic phases of the disease, confirmation of the diagnosis rests on the relative evaluation of several specific laboratory tests: primary isolation of the Brucella organism by cultural methods from the blood, other body fluids or tissues of the patient, indirect recovery of Brucella by culture after animal inoculation, the agglutination reaction, and the intradermal and the opsonocytaphagic tests. The first two procedures are self-explanatory and will not be discussed.

The *agglutination test* is most valuable diagnostically in acute cases. Agglutinins may appear as early as the fifth day but ordinarily do not until ten to fourteen days after the onset of the disease. Agglutination of Brucella antigen to titers of 1:135 is usually considered significant and presumptive evidence of an active infection with typical clinical symptoms. In some cases, particularly of the chronic type, agglutinins cannot be detected throughout the course of the disease. Furthermore, a significant agglutinin titer may not always indicate that the presenting symptoms result from active brucellosis. Agglutinins are present in the blood for many years after an infection. A positive agglutination merely indicates that the organism has successfully invaded the host ten days or more prior to the performance of the test. Furthermore, patients with tularemia may show agglutinins in low titer for Brucella, as may those treated with cholera vaccine (this may be confusing among former servicemen who received cholera prophylaxis) or infected with *Vibrio comma* (*V. cholerae asiaticae*). It has been reported that the serum of 3 to 9 per cent of patients with tuberculosis will give a false-positive reaction to this test, another study, however, has shown that a moderate number of patients with tuberculosis have had undulant fever at some time. Occasionally, cross-agglutination may occur in the presence of infection with *Eberthella typhosa*, *Proteus vulgaris* (X19 strain) and, more rarely, in other infections.

The *intradermal test* is an allergy test detecting sensitization to Brucella. An appropriate Brucella antigen (0.1 cc of "Brucellergen," or 0.02 cc of 1:10 dilution in physiologic saline solution of a bacterial suspension of 4,000,000,000) is injected into the skin of the flexor surface of the forearm. In positive cases, the reaction begins in twenty-four hours, rapidly spreading from 2 to 10 cm in diameter, with erythema, considerable circumscribed edema and pain or itching, all of which may last up to nine days. The local reaction may be accompanied by an exacerbation of symptoms in infected patients and a mild systemic reaction in those hypersensitive to Brucella. A nonspecific reaction may appear within the first twenty-four hours, consisting of an area of erythema 1 to 2 cm in diameter, which is of no significance and is rarely seen at the end of forty-eight hours. A positive cutaneous reaction signifies a past or present infection with Brucella.

It must be strongly stressed that whenever a skin test is to be performed, a blood sample for an agglutination test should be taken *before* the skin test. A false-positive agglutination test in low titer may result when the latter procedure is done after the skin test. This may be due to a previous exposure to the skin-test antigen. Secondly, a skin-test dose of antigen may act as a booster dose, elevating the Brucella agglutinin titer in the serums of previously infected patients to a significant level (even though the titer is not contributing to the pre-

senting illness) Therefore, the intradermal test should be deferred until all information obtainable from the agglutination test has been secured

The *opsonocytophagic test* as developed by Huddleston should be performed within seven days of the onset of the illness. In this procedure equal volumes of the patient's citrated blood and a saline suspension of living *Brucella* are mixed. After thirty minutes of incubation, a smear is made from the centrifuged mixture. The number of bacteria in 25 polymorphonuclear leukocytes is counted. If no cells are found in the leukocytes, the test is negative, if the number is less than 20, the opsonocytophagic power is considered to be slight, if between 20 and 40, it is moderate, and if over 40, it is marked. A positive skin-test reactor is considered infected if less than 50 per cent of cells show marked phagocytosis, questionably infected or immune if 50 to 80 per cent of cells show marked phagocytosis and immune if 80 per cent or more reveal marked phagocytosis. A negative skin test and little or no phagocytic activity indicate susceptibility to infection. It has been noted that patients infected with *Brucella melitensis* frequently show phagocytosis as high as immune subjects, therefore, a high opsonic activity does not always indicate immunity.

Other laboratory procedures have been employed in diagnosis, — namely, the precipitin and complement-fixation tests and various therapeutic tests, — but they have proved to be too inconclusive for wide general use.

No single test considered individually, with the exception of positive culture from the patient or through animal inoculation, is conclusive. All should be evaluated from a relative standpoint, and the results weighed carefully with the history and the clinical picture before a definite diagnosis is made.

Appropriate tests can be used to rule out the confusing diseases mentioned above. Agglutination tests for typhoid and paratyphoid B are routinely performed by the State Diagnostic Laboratory on all blood samples sent in for undulant-fever agglutination. On request, a heterophil-antibody titration for the diagnosis of infectious mononucleosis is done on the same blood.

## CORRESPONDENCE

### EFFECT OF LARGE DOSES OF IRRADIATION ON GASTRIC ACIDITY

To the Editor: The article by Dr Irving B. Brick entitled "The Effect of Large Doses of Irradiation on Gastric Acidity," which appeared in the July 10 issue of the *Journal*, has been read with great interest. However, it seems to me to contain certain fallacies to which attention should be drawn.

In the first place the title and the article itself imply, and, indeed, state that the effect of large doses of irradiation on gastric acidity have been studied. In fact, the "radiation was delivered to the antrum of the stomach rather than to the upper part." It is a well recognized fact that the antrum does not secrete acid juice, the cells secreting acid and pepsin are located in the middle and upper portions of the

stomach. Dr. Brick seems to take cognizance of this fact, but considers it only a "possible explanation." He specifically states that in previous studies using the 10 by 10 cm. portals described "it was shown that the effects both radiographically and pathologically are confined mainly to the antral and pyloric regions" (italics mine). How then can he draw any conclusion regarding the effect of irradiation on gastric secretion when he has not irradiated the acid-secreting portions of the stomach?

Furthermore, I must protest against the sweeping statement in the summary that "the use of radiation has no place in the treatment of peptic ulcer, since it has been shown that deleterious effects on the stomach can be obtained with this agent." Surely the author would not contend that all agents with which "deleterious effects can be obtained" should be removed from our therapeutic armamentarium!

The demonstration by Dr. Brick of antral ulcers in 9 patients after intensive radiation of that region for tumor is important, but it is not pertinent to the problem of peptic ulcer. The lesions seem clearly due to radiation necrosis and are not analogous to spontaneous peptic ulcers. The susceptibility of the gastric and intestinal mucosae, and, indeed, of all living tissue, to irradiation, given in adequate dosage, is well recognized. The fact that radiation may produce tissue necrosis under certain circumstances does not prove radiation to be of no value under other circumstances. Specifically if radiation were able to destroy the acid-secreting cells of the gastric mucosa the procedure might be of very great value in the treatment of peptic ulcer, a disease, by the way, not entirely of "unknown etiology."

I regret the necessity of finding fault with an excellent study. As Professor A. J. Carlson has often said in effect "Facts are never in error regardless of how wrong the interpretation may be." I am sorry that Dr. Brick did not restrict his discussion to the evidence presented.

WAITER L. PALMER, M.D.

Department of Medicine  
University of Chicago

\* \* \*

Dr. Palmer's letter was referred to Dr. Brick, whose reply is as follows:

To the Editor: I wish to thank Dr. Palmer for the interest displayed and the astute criticism of some of the conclusions.

As pointed out in my article, these studies on gastric acidity were made on patients with normal stomachs. The effect of radiation, which was being given for malignant disease extrinsic to the stomach, on gastric acidity was of some interest in determining whether or not the course of radiation injury of the stomach was altered by the degree of gastric acidity. There did not appear to be any correlation of the course and degree of gastric acidity. While, with the technique of irradiation used in these cases, the major portion of the radiation is directed at the antral portion of the stomach, there is undoubtedly overlap of radiation effect of the upper portion of the stomach as demonstrated at operation (Bowers, R. F., and Brick, I. B., *Surgery* 22:20, 1947). The most drastic injury appeared in the antrum and pylorus, but there appeared evidence of radiation effect throughout the stomach in the form of edematous thickening and avascularity. Submucosal edema and cellular changes of a nonspecific nature were noted histologically in sections from the fundus.

More relevant to the discussion is the careful study of Dr. W. L. Palmer and F. Templeton (*J. A. M. A.* 112:1429, 1939) in which dosages of 1100 to 3600 r were directed to the upper portion of the stomach in patients with peptic ulcer. The charts accompanying the article reveal the extreme variability of reaction of gastric acidity to the radiation. One patient receiving 3600 r had a minimum depression of gastric acidity while another receiving only 1097 r had a rather prolonged depression (more than one hundred and sixty days). It is this extreme variability, which we also have encountered not only in the effect on gastric acidity but also in the radiation injury to the stomach, that deserves emphasis. Why some patients can receive 5000 to 6000 r and reveal no evidence of injury to the stomach and another patient receiving a dosage as low as 2424 r with the same technique (as in Case 9 in my article) will develop an ulcer, is a question of individual tissue tolerance to radiation worthy of further study. With the dosages used by Dr. Palmer, in 1 case receiving 2965 r hepatic necrosis was observed at operation and only a moderate depression of gastric acidity was ob-

ained. In another patient who received 3227 r study of the gastric mucosa was possible since the patient died of an entirely unrelated coronary occlusion one day after completion of radiation therapy. The pathologist reported that the mucosa revealed profound alterations everywhere, especially in the fundus. This, too, affords some evidence that there is apparent overlap of the radiation effect since in these cases the radiation was directed only to the upper part of the stomach. Drs Palmer and Templeton made no claim whatever for the efficacy of radiation in the treatment of peptic ulcer, nor did they advocate its use or delineate any place that such treatment might have in peptic ulcer. I have not been able to find in the literature the results of the continuation of this interesting study or any other using the same range of dosage of radiation.

It is from this study of Dr Palmer and from my own that the conclusion that radiation has no place in the treatment of peptic ulcer was drawn. That conclusion should have been qualified by the addition of 'with the dosages of radiation studied.' For with the dosages used both in the cases of Drs. Palmer and Templeton and in my cases the effect on gastric acidity was extremely variable, being unpredictable in the individual case, and the possibility of radiation injury was present. Furthermore we are sure that over a longer period of observation there might not be progressive changes due to radiation? The well known progression and complications of x-ray skin burns may be an instance in analogy.

I can only agree with Dr Palmer that if radiation were able to destroy the acid-secreting cells of the gastric mucosa the procedure might be of great value in the treatment of peptic ulcer, but hasten to add that the dosage must be a safe one free of potentially serious dangers in the treatment of a disease in which the group with which Dr Palmer is associated has had notable success by means of methods other than radiation. I believe that with the present knowledge of radiation effect on the stomach with and without peptic ulcer the use of radiation in the treatment of peptic ulcer should be limited to investigative personnel doing carefully controlled clinical research as illustrated notably by Dr Palmer and associates. To date no one has claimed to be able to produce destruction of the acid-secreting cells of the gastric mucosa with radiation regardless of dosage.

In closing I should like to call attention to a paper not available to me at the time of publication of my article in the *Journal*. Drs. Palmer, Levin and Hamann (*Gastroenterology* 8:565 1947) using dosages of radiation varying from 1350 to 1710 r over the body and fundus of the stomach studied the effect on nocturnal gastric secretion in patients with duodenal ulcer. No toxic effects were noted. The variability of depression of gastric secretion in the period studied (fourteen to one hundred and fifty days) is again pointed out. Since the patients had received antacid therapy prior to radiation this is not a strictly controlled study. No claim is made for the use of radiation in the treatment of peptic ulcer.

It is hoped that cases studied over a longer period will be available to determine the effect of safe radiation dosages on the chronic recurring disease that is peptic ulcer. Such a study may properly lead to a more adequate evaluation of the place that radiation holds in the therapy of peptic ulcer than I have been able to conclude from the available data.

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## BOOK REVIEWS

*Penicillin in Neurology*. By A. Earl Walker, M.D. and Herbert C. Johnson, M.D. 8 cloth 202 pp. with 72 illustrations. Springfield, Illinois: Charles C. Thomas, 1946. \$5.00.

When penicillin was discovered as a therapeutic agent it was at once suggested as having probable value in diseases of the nervous system, particularly those due to infections. Although relatively nontoxic when given parenterally, the drug was not so innocuous when applied directly to the nervous system. If injected subcutaneously it did not reach the cerebrospinal fluid. Thus, for the treatment of meningitis and some infections the drug had to be put directly into the intrathecal space. An effort was made, moreover, to apply it directly to the nervous system, particularly the brain when

exposed by surgical means. The authors, who at the time this book was compiled were in the United States Army, had wide experience in the use of penicillin. Dr. Walker was at the Cushing General Hospital and Dr. Johnson served at the Lawson General Hospital.

Penicillin is somewhat toxic when given intrathecally or placed directly on the cerebral cortex. In this monograph the reactions are described both in man and in animals and the indications for its clinical use are set forth in a clear manner. Time has changed the situation slightly, but the fundamental investigations reported in this work are still sound. Brief consideration is given to the treatment of syphilis of the nervous system and to the use of other antibiotic substances. The bibliography is adequate, and the illustrations are good. There is an adequate index. Since the book was written in the midst of active investigations and during a period of stress owing to wartime activities it cannot be considered a final report on the use of penicillin in the treatment of neurologic disorders. The monograph is strongest in the field of neurosurgery and relatively weak in that of the treatment of nonsurgical disorders.

*Military Neuropsychiatry*. Volume XXV of the *Proceedings of the Association for Research in Nervous and Mental Diseases*. 8° cloth 366 pp. Baltimore: Williams and Wilkins Company, 1946. \$6.00.

The subject of military neuropsychiatry is reviewed by over forty-five investigators, most of whom were active participants in World War II. Practically all aspects of the subject are covered by the papers read and discussed at the annual session in December, 1944 of the Association for Research in Nervous and Mental Disease. Since the contributions were written in 1944 the later developments in 1945 are not covered. The volume sets a high standard and is useful as a record of papers in understanding the problems of the war neuroses, combat exhaustion, the psychotherapy of the soldier during conflict, the therapeutic use of drugs in narcosis, anesthetic, craniocerebral injuries and the electroencephalogram, convalescent reconditioning and rehabilitation of discharged veterans. The authors include John E. Whitcomb, Roy R. Grinker, William C. Menninger, Howard P. Rome, Barnes Woodhall and Lewis J. Pollock. As usual in this series of volumes the book is well edited and printed.

*Fundamentals of Clinical Neurology*. By H. Houston Merritt, M.D., Fred A. Mettler, M.D., Ph.D. and Tracy J. Putnam, M.D. 8° cloth 289 pp. with 96 illustrations. Philadelphia: Blakiston Company, 1947. \$6.00.

The authors have attempted to give in two sections of the book an outline in some detail of the clinical examination of the nervous system and the methods used in arriving at a correct anatomic diagnosis in cases of structural diseases. In both endeavors they are successful for this is a sound text considering the limitations set up by the three men who collaborated in writing it. One is a clinical neurologist, another an anatomist and the third a neurosurgeon. The book is designed for the use of practitioners and presumably for students of medicine. There are no references to the literature other than an occasional note on the source of an illustration. Although the book contains no material that could not easily be discovered in current texts on clinical neurology, the book will prove to be useful. Some of the illustrations being clear line drawings are of particular value. The section on the examination of the nervous system is good and seems suitable to the aim of the book, that on anatomic diagnosis which is far in advance of the general practitioner or beginning student, promises to be useful only for postgraduate students in neurology and indeed often goes beyond the material needed for anyone practicing that specialty. Because of this unevenness the book cannot be highly recommended. The authors have put together two unequal parts of clinical neurology overfilling the pages with detailed anatomy much to the detriment of the book as a whole.

*A Handbook of Commonly Used Drugs including Certain Measures for the Control of Diseases Peculiar to the Tropics of the Western Hemisphere*. By Michel Pijon, M.D. and Charles H. Yeager, M.D., Dr. P.H. 8° cloth 198 pp. Springfield, Illinois: Charles C. Thomas, 1947. \$3.75.

This small book is largely compiled from personal experiences in the use of drugs, particularly in the tropics. It is a



condensation of larger works on the pharmacologic basis of therapeutics. Sound and clearly written, the volume should be of use. Although published this year, it is already outdated in certain aspects of the subject. To be of value, such a book should become a continuous product, the authors working on a subsequent edition even before the current one is published. A volume should probably be issued at least every three years. For example, most of the references used in the present book refer to articles published before 1940. In the section on endocrines there is no reference to the literature beyond that date, and yet the title page indicates that the purchaser is justified in expecting the literature to be covered at least through 1946. An even worse record is made in the reference under the therapy of syphilis, for the only work cited is one issued by the same publisher, an edition of 1933. This book, therefore, although valuable and well written, needs complete revision to bring it up to date.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Standard Methods of the Division of Laboratories and Research of the New York State Department of Health.* By Augustus B. Wadsworth, M.D. With a foreword by Gilbert Dalldorf, M.D. Third edition. 8°, cloth, 990 pp., with 109 illustrations. Baltimore: Williams and Wilkins Company, 1947. \$10.00.

This third edition of a standard reference work has been revised to include changes and additions made from 1939 to January 31, 1945, when Dr. Wadsworth retired from service. Changes will be noted in practically all sections of the text. A complete revision has been made in the routine methods for the serodiagnosis of syphilis. An outstanding change is the substitution of a new antigen composed of cardiophin, lecithin and cholesterol for the cholesterolized alcoholic extract of beef heart that had been in use for several years. Certain methods in the fields of biochemistry and biophysics have been revised, and new procedures, as well as a new chapter on biologic assay, have been added. In the preface Dr. Wadsworth has given a brief history of the organization under which the methods outlined in the book have been formulated. The volume is recommended as a reference work for all medical laboratories and libraries.

*Rehabilitation through Better Nutrition.* University of Cincinnati Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama. 8°, cloth, 94 pp., with fifty illustrations, some in color. Philadelphia: W. B. Saunders Company, 1947. \$4.00.

This monograph summarizes the work carried on successfully since 1930 on persons suffering from deficiency diseases and treated by long-term nutrition therapy. It points out that malnourishment usually develops over a period of months or even years and that adequate results from nutritive therapy necessitate long treatment in many cases. From 1930 to 1936 the author studied 278 patients in Ohio with lesions typical of pellagra, beriberi or scurvy. In the Birmingham Clinic 914 patients suffering from various deficiency diseases were selected for study. These patients were afflicted with the vitamin deficiencies, including pellagra and scurvy, the various anemias with nutritive failure, non-tropical sprue and protein deficiency.

Emphasis is placed on accurate diagnosis, and the first part of the monograph is devoted to a discussion of the various diseases from this point of view. A total of 10,851 persons were examined in the clinic from 1936 to 1945, and no evidence of nutritive failure was found in 5140 cases. From the remainder 914 patients with general nutritive failure severe enough to keep them from work were selected. At the final check-up examination in 1945, 21 were not available for various reasons, and the final study was therefore based on 893 cases. It is interesting that the Whites outnumbered the Negroes about 11 to 1, although the population of the community was equally divided.

All the patients included in the study improved promptly under the special treatment, gaining strength and weight, and were able to return to work, which they continued regularly.

The treatment consisted essentially of a high-calorie diet, supplemented by proteins, vitamins and minerals.

The principles of therapy used successfully in these cases were as follows: conditions causing excessive requirements were removed or relieved whenever possible, symptomatic treatment and therapy for coexisting diseases were given, it was made certain that the patient consumed daily a diet that supplied 3000 to 4000 calories, 120 to 150 gm. of protein and liberal amounts of minerals and vitamins, and therapeutic substances, such as dried brewer's yeast powder, liver extract and synthetic vitamins, were administered in sufficient amounts to correct the deficiency. It cannot be expected that these principles will be effective if the diagnosis is not precise or if the therapy is not persistently applied.

The text is well documented with tables, charts and case histories. The illustrations are excellent. A list of references concludes the text. The volume is well published in every way and is recommended for all medical libraries and to all physicians interested in deficiency diseases.

*Diseases of the Nervous System.* By F. M. R. Walshe, M.D., D.Sc., F.R.C.P. (Lond.), F.R.S., physician-in-charge, Neurological Department, University College Hospital, London, and physician, National Hospital for Nervous Diseases. Fifth edition. 8°, cloth, 351 pp., with 59 illustrations. Baltimore: Williams and Wilkins Company, 1947. (Printed in Great Britain.) \$4.50.

The soundness and popularity of this small textbook is attested by the need of five editions in six years. The text has been brought up to date. The chapters on intracranial tumors and cerebral vascular disease have been rewritten. The volume is printed with a good type on good paper and, for the first time since the war, has wide margins pleasing to the eye.

## NOTICES

### AMERICAN ASSOCIATION ON MENTAL DEFICIENCY

The Northeastern Section of the American Association on Mental Deficiency will hold a meeting at the Wassaic State School, Wassaic, New York, on Saturday, October 18. After inspection of the school, followed by luncheon at 12:30 p.m., a regular meeting will be held.

#### PROGRAM

- An Analysis of the Relationship of the Moron Group to State School Training. Drs. Ernest S. Steblen and Joseph E. Rosenfeld.
- Social Service in the Realm of Mental Deficiency. Patricia F. Morgan.
- Occupational Therapy with Mental Defectives. Percy H. Larrabee.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 16

- FRIDAY, OCTOBER 17
  - \*9:00-10:00 a.m. Gastritis. Dr. Seymour Gray. Joseph H. Pratt. Diagnostic Hospital.
  - \*10:00 a.m.-12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.
- MONDAY, OCTOBER 20
  - \*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.
- TUESDAY, OCTOBER 21
  - \*12:15-1:15 p.m. Clinicorontgenological Conference. Peter Bent Brigham Hospital.
- WEDNESDAY, OCTOBER 22
  - \*9:00-10:00 a.m. Uterine Retrodisplacements. Dr. George A. Bear. Joseph H. Pratt Diagnostic Hospital.
  - \*12:00 m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*Open to the medical profession.

(Notices continued on page xv)

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## CLINICAL SIGNIFICANCE OF MALIGNANT NEOPLASMS OF THE THYROID GLAND\*

WALTER F. ROGERS, JR., M.D.,† SAMUEL P. ASPER, JR., M.D.,‡ AND ROBERT H. WILLIAMS, M.D.§

BOSTON

THE value of extirpating goiters, particularly nodular ones, for the prevention of malignant neoplasms of the thyroid gland has been the subject of considerable discussion for many years. Opinions have ranged from a conservative attitude to one of removing all goiters containing nodules, whether single or multiple.<sup>1,2</sup> In the presence of these divergent opinions, the frequency with which prophylactic thyroidectomies should be performed needs evaluation.

There are numerous reports in the literature concerning the incidence of malignant neoplasms of the thyroid gland.<sup>1-7</sup> In two recent reports the incidence of carcinoma was particularly high, Cole et al.<sup>1</sup> stating that the incidence was 17.1 per cent in patients with nontoxic nodular goiters, including those with single or multiple nodules, and 7.2 per cent in all nodular goiters, toxic and nontoxic. Such statistics raise an enormous problem if thyroidectomy is to be advocated for all people with nodular goiters, particularly when one considers that in an endemic area the incidence of nodular goiters has been shown to be 80 per cent in autopsy material.<sup>2</sup> Even in nonendemic areas, such as the New England seaboard, Schlesinger and his associates<sup>4</sup> found thyroid nodules, 1 cm. or more in size, which should be clinically palpable, in 82 per cent of cases at autopsy. Using the figures of Cole et al.,<sup>1</sup> one might then expect that from 5 to 13 per cent of the people living in an endemic area would suffer from carcinoma of the thyroid gland and that in a nonendemic area the incidence would be from 0.5 to 1.0 per cent.

These hypothetical data show wide discrepancies from actual figures, for in two large series of routine autopsies thyroid carcinoma was found in 1.04 per

cent<sup>3</sup> and 1.07 per cent<sup>4</sup> in endemic areas and in 0.095 per cent<sup>5</sup> and 0.109 per cent<sup>6</sup> in nonendemic areas. In 74,335 cases at autopsy in the United States and Europe, tabulated by Wilson,<sup>4</sup> the incidence was 0.26 per cent.

Thus, diagnoses of malignant neoplasms of the thyroid gland appear to be frequent in surgical specimens but rare in clinical and autopsy material. The advisability of removing all nontoxic nodular goiters to eradicate a few potentially cancerous glands should be critically considered along with the mortality and complications resulting from these operations. In addition, the actual effect of so-called "prophylactic surgery" on malignant neoplasms of the thyroid gland should be evaluated.

To help clarify this problem, we reviewed the records of patients with goiter admitted to the Boston City Hospital, the Johns Hopkins Hospital, and the Massachusetts General Hospital in twelve-year (1931-1942), five-year (1940-1944) and eight-year (1937-1944) periods, respectively. The clinical course and pathological lesions in cases of malignant neoplasm of the thyroid gland, diagnosed histologically on autopsy or surgical material, were analyzed. These patients have subsequently been followed for from one and a half to ten years. In addition, the records of 431 patients who had undergone operations for nonmalignant, nontoxic goiter were studied to determine the mortality and complications of this operation.

The large size and location of these general hospitals and the cross section of patients treated should give a good indication of the significance of thyroid cancer in a nonendemic area.

The total number of admissions to the three hospitals in the periods analyzed was 544,918, and goiters were observed in 3221 cases (Table 1). This incidence of goiter, 0.59 per cent, was extremely low and is best explained by the fact that the cases were taken from all the services of large general hospitals and that the neck was not carefully examined in all patients. Table 1 also presents the number of

\*These operations were performed at the Boston City and Johns Hopkins hospitals.

\*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital and the Department of Medicine, Harvard Medical School.

†Research fellow in medicine, Harvard Medical School; research fellow in medicine, Thorndike Memorial Laboratory and assistant in medicine, Boston City Hospital.

‡Assistant in medicine, Harvard Medical School; research fellow in medicine, Thorndike Memorial Laboratory and assistant in medicine, Boston City Hospital.

§Assistant professor of medicine, Harvard Medical School; assistant physician, Thorndike Memorial Laboratory and junior visiting physician, Boston City Hospital.

nodular and diffuse goiters and the incidence of thyrotoxicity

A pathological diagnosis of malignant neoplasm of the thyroid gland was made in 64 cases, or in 1.99 per cent of all the patients with goiter. Ten additional cases of what appeared to be far-advanced

Of the 64 patients, 76 per cent were females, and 24 per cent were males. This ratio of 3:1 is lower than the usual ratio in nonendemic areas, which is estimated to be 6:1 or 7:1.<sup>8</sup>

The patients complained of a variety of symptoms (Table 2). Fifty-five patients, or 86 per cent, with

TABLE 1 Incidence of Goiters and Malignant Thyroid Neoplasms

SOURCE OF DATA	HOSPITAL ADMISSIONS	ALL GOITERS	TOXIC GOITERS			NONTOXIC GOITERS			MALIGNANT THYROID NEOPLASMS
			UNSPECIFIED TYPE	NODULAR TYPE	DIFFUSE TYPE	UNSPECIFIED TYPE	NODULAR TYPE	DIFFUSE TYPE	
Boston City Hospital	406,402	1,125	—	125	306	16	551	127	17
Massachusetts General Hospital	61,117	1,379	—	180	391	—	751	57	27
Johns Hopkins Hospital	77,399	717	24	72	210	34	161	216	30
Totals	544,918	3,221†	24	377	907	50	1,463	400	74‡

\*Not confirmed by histologic examination, but clinical course compatible with diagnosis.

†0.59 per cent of total hospital admissions.

‡0.0136 per cent of total hospital admissions and 2.29 per cent of all goiters.

malignant neoplasms of the thyroid gland were not proved histologically, inclusion of these cases makes an incidence of 2.29 per cent in patients with goiter. In the following analysis of cases only those with a

malignant neoplasm of the thyroid gland noted a mass or enlargement of the neck. Further elucidation of the history of the mass, however, was important. In the charts of the 55 patients who had noted a mass in the neck, there was a definite statement in 43 cases regarding whether the patient or a physician had noticed a change in the size of the mass before admission. Thirty-four, or 79 per cent, of the 43 patients had noticed a recent progressive increase in the size of the goiter.

None of the other symptoms was experienced in more than 20 per cent of the patients. Aside from

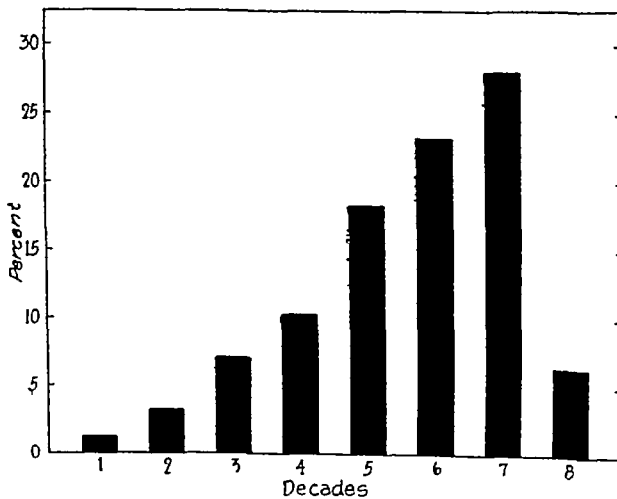


FIGURE 1 Age of the Patient at the Time of Diagnosis

histologic diagnosis of a malignant neoplasm are included.

Cancer of the thyroid gland occurred in each of the first eight decades, with constant increments up to the seventh decade, in which 18 of the 64 cases (28.2 per cent) were found (Fig. 1). There were relatively few cases in the eighth decade. Although there was no significant difference between the average ages of the male and female patients, the former being fifty-three and a half and the latter fifty years, there were only 3 males under the age of fifty, whereas 22 females were below that age.

TABLE 2 Symptoms in 64 Cases of Malignant Neoplasm of the Thyroid Gland

SYMPTOM	NUMBER OF PATIENTS	PERCENTAGE
Mass or enlargement of neck	55	86.0
Hoarseness	12	18.7
Dyspnea	12	18.7
Dysphagia	9	14.0
Bone pain (metastatic lesions)	8	12.5
Nervousness	7	10.9
Cough	6	9.4
Weight loss	3	4.7
Palpitation	2	3.1
Paralysis of lower extremities (metastatic lesions)	1	1.55
Hyperorexia	1	1.55
Headache	1	1.55
Irritability	1	1.55
Dizziness and faintness	1	1.55
Chest pain	1	1.55

struma, the most frequent symptoms were those of compression of the surrounding structures: hoarseness, dyspnea and dysphagia. Pain in association with metastases to bone occurred in 12.5 per cent of cases. Although a great variety of other complaints were made, these were infrequent and not usually of much aid diagnostically. No patient had symptoms of hypothyroidism.

There was a palpable mass in the neck of 63 patients, or 98 per cent. In 47 cases (73.4 per cent) the masses were nodular in contour, and of these, 37, or 78.7 per cent, had a single nodule, 5 cases were multinodular, and in 5 the exact nature of the mass could not be ascertained. The remaining 17 patients had a diffuse type of struma.

The next most frequent physical sign was enlargement of the cervical and supraclavicular lymph nodes, the former occurring in 23.4 per cent of cases and the latter in 7.8 per cent. Other less common signs were paralysis of the vocal cords, increased areas of retromanubrial dullness, masses in the skeleton and neurologic disturbances. No patient had evidence of hypothyroidism.

In an attempt to analyze the extent of metastases, the course, the mortality and the prognosis of pa-

six per cent of cases were classed in the highly malignant group, whereas those designated as low malignancy were relatively infrequent.

Figure 3 presents the extent of involvement in relation to the cervical lymph nodes with subdivision

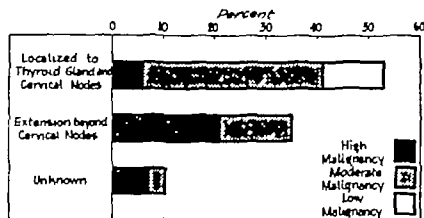


FIGURE 3 Extent of Spread of Neoplasms

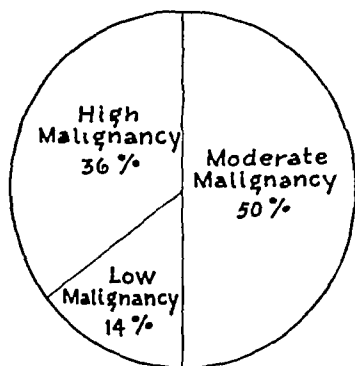


FIGURE 2 Degrees of Malignancy

into the respective degrees of malignancy. In 53 per cent of cases the neoplasm was localized to the thyroid gland and cervical lymph nodes, whereas in 36 per cent it had extended beyond this point. In 11 per cent the extent of the lesion could not be exactly evaluated, and the involvement in such cases was classed as "unknown."

It should be noted that the majority of cases with the neoplasms localized to the thyroid gland and

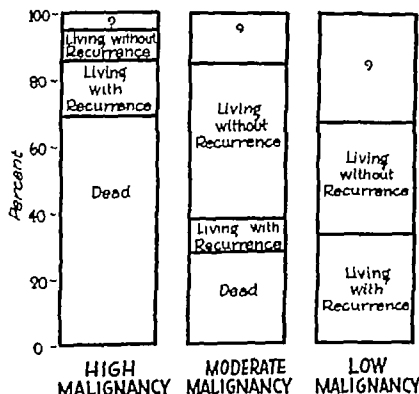


FIGURE 4 Course of Patients in Relation to the Degree of Malignancy

tients with malignant neoplasms of the thyroid gland, it is most important to consider the pathologic classification of these tumors. Lahey, Hare and Warren<sup>8</sup> reported a classification that is extremely useful, the degrees of malignancy being classified as high, moderate and low. The first group included cases of carcinoma simplex, giant-cell carcinoma, epidermoid carcinoma, fibrosarcoma and lymphosarcoma. In our study the patients with a diagnosis of carcinoma (unclassified) have also been placed in this group. The group classed as moderately malignant consisted of papillary adenocarcinoma, alveolar carcinoma and Hürtle-cell adenocarcinoma. The last and least malignant group was made up of adenoma and papillary cystadenoma with blood-vessel invasion.

In this series the proportion of cases falling into the respective groups is shown, and it may be noted that half the 64 cases occurred in the group considered to be moderately malignant (Fig. 2). Thirty-

cervical lymph nodes were classed as "moderately malignant" (Fig. 3). It is still more striking, however, that all the cases of low malignancy were localized to this region. On the other hand, a relatively small number of the highly malignant lesions were limited to the cervical nodes.

Over half the patients with widespread disease were designated as having highly malignant tumors, and the remainder of cases were classed as moderately malignant. The group classed as unknown were composed mostly of patients with highly malignant tumors. The majority of these patients had large masses in the necks at the time of death, but no permission for autopsy was obtained and the extent of the disease could not be accurately determined.

The mortality was 37.5 per cent, the maximum time of follow-up study being ten and the minimum one and a half years. Of the remaining patients

number living with and without recurrence was equal. As the degree of malignancy declined, less was known about the fate of the patients, probably owing to the fewer symptoms in the patients with more benign lesions, who failed to return for follow-up study.

The duration of goiters before the diagnosis of cancer and the duration of the lesions after diagnosis in patients with highly and moderately malignant tumors is shown in Figure 5. Some patients with highly malignant neoplasms had long-standing goiters, but a large number had goiters of less than one year's duration. In the patients with moderately malignant lesions the goiters were of longer duration, and 15 patients, or 55.5 per cent, had goiters ranging from three to forty years. Likewise, the duration of the disease after the diagnosis had been established was usually less than two years in the highly malignant cases, whereas that in the moderately malignant cases was usually longer than two years. The duration in cases of malignant neoplasm was determined only in the patients who had died or were living with recurrence. Consequently, there is a discrepancy in the number with moderately malignant tumors, because many of these patients are living without recurrence.

To emphasize the varied course that malignant neoplasms of the thyroid may pursue, the following brief abstracts of case reports are presented.

**CASE 1 (BCH 1,011,410)** A 52-year-old woman was admitted to the Massachusetts Memorial Hospitals in January, 1941, with the chief complaint of a mass over the right eye of 5 months' duration. There was no history of previous goiter. Physical examination revealed a firm mass, 2.5 by 1 cm in diameter, over the right eye, and a nodule protruding upward from beneath the manubrium of the sternum that was thought to be an adenoma of the thyroid gland. The substernal nodule and a portion of the cranial nodule were removed. The histologic diagnosis of the former was small-cell carcinoma arising from an embryonal adenoma, and the mass in the cranium was reported as metastatic carcinoma of the thyroid gland. The patient was then transferred to the Boston City Hospital, where the skull lesion was resected. After operation, she made an uneventful recovery and was well for 5 years, when there was evidence of recurrence of the tumor in the skull. X-ray therapy effected some regression of the lesion. Otherwise, the patient has remained in good health.

**CASE 2 (MGH 161,672)** In 1928 a 53-year-old woman was admitted to the hospital complaining of a mass at the medial end of the left clavicle. This was removed and was diagnosed as a carcinoma arising in the thyroid gland. After the excision, the patient did well for 11 years, when she began to complain of hoarseness and swelling of the neck, accompanied by pain in the right clavicle and chest. Physical examination at that time revealed a pulsating tumor mass, the size of a hen's egg, at the medial end of the right clavicle. In addition, there were some small nodules surrounding the mass. A biopsy specimen, obtained by needle, was diagnosed as a rapidly growing fetal adenoma, and an x-ray film of the chest was consistent with metastatic cancer. The patient was given x-ray therapy to the right side of the neck and upper mediastinum, with a decrease in the size of the masses in both areas. General improvement followed, and for the next 5 years the patient remained well except for slow growth of the mass in the right side of the neck. At the end of that period she also had pain in the right arm and a destructive lesion in the ilium. She received x-ray therapy to the

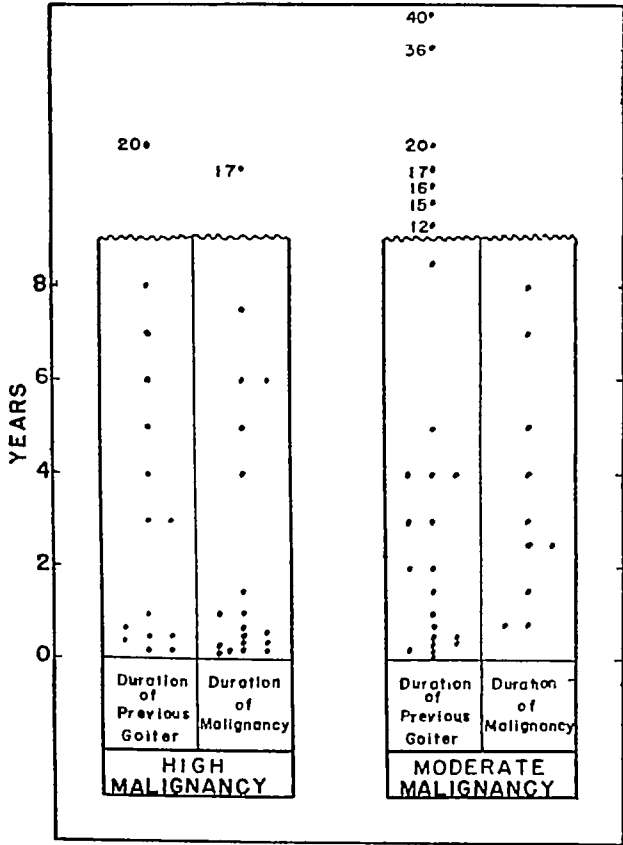


FIGURE 5 Duration of the Goiter previous to the Diagnosis of Malignancy and the Duration of the Malignancy in Patients Who Died or Were Living with Recurrence

15.5 per cent are living with recurrence, 31.2 per cent are living without recurrence, the fate of 12.5 per cent is unknown, and 3.3 per cent died of intercurrent disease. More revealing, however, is the course of the patients in relation to the degree of malignancy (Fig. 4). It is seen that 69 per cent of patients with highly malignant tumors are dead and that 17.4 per cent of the others had a recurrence of the disease. In the moderately malignant group, the largest share are living without recurrence, whereas 38 per cent are dead or living with recurrence. Among those with tumors of a low degree of malignancy, there were no deaths, but the

mass in the neck and to the lesion in the ilium without any noticeable clinical improvement. Five months later she died at home, 17 years after the initial diagnosis of carcinoma had been made.

These cases illustrate the long course that carcinoma of the thyroid gland may take, despite the presence of widespread metastatic lesions.

On the other hand, some patients pursued a rapidly fatal course as in the following case.

**CASE 3 (M.G.H. 466,945).** A 58-year-old man entered the hospital complaining of hoarseness and headaches of 3 months' duration, accompanied by weight loss. There was no history of goiter. Physical examination showed a swelling of the right side of the neck, with a hard irregular mass involving the thyroid gland and extending superiorly and attached to the deep structures. In the hospital he rapidly became worse and shortly after admission contracted an upper respiratory infection followed by pneumonia and death. Autopsy revealed a small-cell carcinoma of the thyroid, with metastatic lesions in the brain, kidneys, adrenal glands and cervical lymph nodes. The entire course of the illness was less than 4 months.

The correct diagnosis was made clinically, or was suspected, in 31 (48 per cent) cases in this series. As would be expected, the correct diagnosis was made more frequently in patients with highly malignant tumors. In the cases in which a correct clinical diagnosis was made 48.5 per cent of patients are dead, whereas in those in which the diagnosis was benign lesions of the thyroid gland, 24 per cent are dead.

Thyroid cancer accompanying thyrotoxicosis is considered rare. In 168 cases of thyroid cancer Ward<sup>1</sup> found 1 case of carcinoma in "a diffuse toxic goiter." Cnle<sup>10</sup> observed 1 case of hyperthyroidism in 249 cases of malignant thyroid neoplasm, and Means<sup>4</sup> stated that thyrotoxicosis might almost be considered insurance against cancer of the thyroid gland.

Five (7.8 per cent) of the 64 patients with malignant thyroid neoplasms had thyrotoxicosis. These cases occurred among 1308 patients admitted with hyperthyroidism during the respective time intervals reviewed, making an incidence of malignant neoplasms of the thyroid gland among thyrotoxic patients of 0.38 per cent. In none of the 5 cases was cancer suspected, and all patients had thyrotoxicosis at the time of operation. All the patients were in the sixth and seventh decades, however, and all were women. The degree of thyrotoxicosis was variable, since 3 cases were considered moderate, 1 severe and 1 mild. Two patients had diffusely enlarged glands without nodules, 2 had diffusely enlarged glands with single nodules, and the remaining case had nodular enlargement of the thyroid gland. The pathological picture in these cases was varied, since 3 were diagnosed as carcinoma (unclassified), 1 as giant-cell carcinoma and 1 as cystadenocarcinoma. The patient with cystadenocarcinoma is living without evidence of recurrence, whereas the patient with the giant-cell carcinoma had a recurrence of the disease, although at present she is in fairly good health. Of the 3 patients with

unclassified carcinoma 1 died with extensive metastases, and the remainder are apparently well despite the fact that the surgical specimens showed invasion of the veins with tumor in 1 case and the presence of a metastatic lesion in a cervical lymph node in the other.

Since thyroidectomy is frequently advocated for "prophylaxis" against cancer, it is of particular interest to determine the effectiveness of this principle in patients in whom there was no clinical suspicion of cancer before operation.

These patients may be divided into two groups: those who, so far as could be ascertained, had no evidence of neoplastic disease at the time of initial operation and who later developed cancer, and those who were not suspected of having malignant lesions until the specimens had been examined by the pathologist.

The first group is composed of 7 patients who had similar clinical courses in that they had had operations for a goiter at some previous date. This operation was followed by a recurrence of the mass, which at a second operation proved to be the site of a malignant process. In 5 patients the neoplastic disease was found twelve, thirteen, sixteen, twenty-four and thirty-four years after the initial operation. Adenocarcinoma was noted in 3 patients, and papillary adenocarcinoma in the other 2. Two patients died of intercurrent disease, 2 are living without recurrence, and 1 is living with a recur-

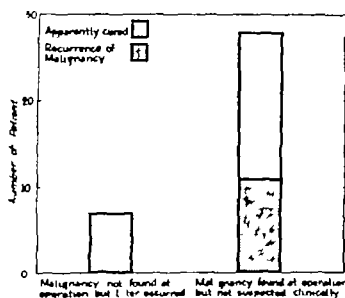


FIGURE 6. Patients in Whom a Malignant Neoplasm Was Not Suspected but in Whom a Thyroidectomy Was Performed

recurrence of the disease. It might be said that these were cases of low-grade malignancy and that the initial operation had been inadequate or that the surgical specimen was not examined carefully enough. This is granted, since in some cases there was no way to determine how thoroughly the initial specimen had been examined. This does not negate the fact, however, that these patients had carcinoma despite prophylactic surgery, and there is reasonably

good evidence that malignant lesions had not been present at the initial operations

An illustrative case is the following

CASE 4 (BCH 906,993) A 62-year-old woman entered the hospital because of recurrent masses in the neck. Twelve years previously she had had a resection of an adenoma at the Lahey Clinic, the specimen having been diagnosed as papillary cystadenoma. Twelve and 14 years, respectively, after operation she entered the Boston City Hospital for recurrent masses in the neck, ranging from the size of a pea to that of a golf ball. These nodules were removed and each time were found to be papillary adenocarcinoma. On the last hospital admission, 16 years after the initial operation, she was admitted for bloody stools, and a diagnosis of carcinoma of the rectum was made. She still had a nodule in the neck, 4 cm in diameter. An abdominal laparotomy and resection of the rectum were advised, but the patient refused operation. She later died at home, apparently from carcinoma of the rectum.

Of the remaining patients in this group, 1 underwent the extirpation of a thyroglossal-duct cyst, and ten months later a mass recurred, was assumed to be a recurrent thyroglossal duct cyst and at operation was found to be a papillary adenocarcinoma of the thyroid gland, the other patient was operated on for an adenocarcinoma of the thyroid gland nine months after the removal of a fetal adenoma. It seems probable that at the time of the first operation each of these patients harbored a malignant neoplasm that was overlooked.

The second group is composed of the 28 patients who were not suspected of having malignant neo-

in mind that the complications in these cases were probably more frequent than those in a series of cases in which all goiters were routinely removed.

There were 5 fatal cases, or a mortality of 116 per cent. The majority of these cases, however, had features that greatly increased the hazard of operation. Thus, 2 patients had dyspnea, dysphagia and pressure symptoms, caused in 1 case by a Riedel's struma and in the other by a large adenoma (10 x 10 x 15 cm) with abscess formation. The glands were removed with great difficulty in both cases. The first patient died on the fourth postoperative day, with an autopsy diagnosis of bronchopneumonia and damage to the recurrent laryngeal nerves, and the second died on the first postoperative day with a clinical diagnosis of pulmonary embolism. A third patient was found to have substernal extension from a nodular goiter and died on the first postoperative day, having become flushed, toxic and delirious. The clinical impression was that the patient died of pneumonia, but autopsy was not performed.

A seventy-three-year-old woman with a 7.5-cm nodule in the right lobe died on the third postoperative day of pneumonia and cardiac failure. Another female patient, aged sixty-one years, had a nodular goiter removed without great difficulty, but it was noted at operation that the trachea was the size of the surgeon's fifth finger. Postoperatively, the patient had respiratory distress and difficulty in speaking, and she died during the second postoperative day.

The various complications of operations on patients with nontoxic goiter are presented in Table 3, of these patients, 15.3 per cent suffered from one or more operative complications, the most significant of which consisted of 13 cases of vocal-cord paralysis, 7 of hypoparathyroidism and 5 of hypothyroidism. Complications such as massive hemorrhage, hematomas and anesthetic accidents, of course, did not involve long-term disability, but at the time caused a definite threat to life.

## DISCUSSION

It is admittedly difficult to determine when a goiter contains a malignant neoplasm particularly a neoplasm that arises in a previously existing adenoma or one of low malignancy. Because of this problem, it has been suggested that every nodular goiter should be "prophylactically" removed.<sup>1,2</sup> This type of reasoning is not regarded as justified, particularly in the light of the figures presented above. Some selection of cases is considered possible, and prophylactic surgery is not reducing deaths from malignant neoplasms of the thyroid gland as much as has been implied.

We have found the clinical incidence of malignant neoplasms of the thyroid gland to be low—much lower in fact than one would expect from previously cited figures on surgical specimens.<sup>2,7</sup>

TABLE 3 Complications of Operations in 431 Cases of Nontoxic Goiter

COMPLICATION	NO. OF CASES	COMMENT
Vocal-cord paralysis	13	Four patients had large glands, and 1 had Hashimoto's disease
Wound infection	11	—
Hoarseness	10	Duration of 3 days to 2 months
Marked swelling of neck, with fever	9	—
Hypoparathyroidism	7	Transient in 5 cases, duration of 1 year or longer in 2.
Hypothyroidism	5	One patient had chronic thyroiditis
Hematoma	3	—
Postoperative hysteria or delirium, or both	3	—
Massive hemorrhage	2	—
Dysphagia	2	Transient but severe
Anesthetic accident	1	Cardiac arrest, restoration of cardiac function with intracardiac adrenalin
Total	66 (15.3%)	

plasms until after histologic examinations of thyroid tissue had been made (Fig. 6). Among these there were 11 who had a recurrence of the tumor, with 6 subsequent deaths.

The two groups of cases discussed above lend support to the statement of Hertz<sup>11</sup> that after multiple operations on thyroid glands, cancer has developed despite the "prophylactic surgery."

To evaluate the principle of the extirpation of goiters, the complications resulting from such a procedure were determined by a review of the charts of 431 patients who had had a thyroidectomy for nontoxic goiters, diffuse or nodular. It was borne

In this report, particular stress has been placed on the pathological lesion and its degree of malignancy because the clinical course of the patient depends so much on this factor. The majority of patients who died of malignant neoplasms of the thyroid gland or had widespread extension had tumors that were classed as highly malignant. These highly malignant tumors, as emphasized by Clute and Warren,<sup>12</sup> were usually characterized by a sudden appearance of a mass in the neck, although at times they arose in a previous goiter, and pursued a rapidly fatal course. Such tumors are rarely removed completely by prophylactic surgery.

On the other hand, in the cases classed as tumors of moderate or low malignancy there were few deaths (none in the latter), and the results of treatment were fairly satisfactory. Even when clinically suggestive of malignancy, these tumors are often amenable to treatment. This point of view is likewise held by Pemberton.<sup>13</sup> These tumors, then, with a better prognosis, are frequently said to be "cured" by prophylactic surgery. When one considers, however, that even when a benign tumor of the thyroid gland or a clinically unsuspected malignant neoplasm is removed, development or recurrence of a malignant neoplasm is not infrequent, the value of routine prophylactic surgery on all nodular thyroid glands becomes less impressive.

As in other reported series, the patients in whom a correct diagnosis was made had the highest mortality rate. This does not necessarily mean that prophylactic surgery would have obviated this, because as pointed out above, the majority of these patients had highly malignant types of tumors in which the onset and course of the disease was of short duration, despite various types of therapy.

The incidence of operative complications in cases of nontoxic goiters should also be considered. If the 431 cases in this report are considered to be an average illustrative example, it is seen that many operative complications and even death may occur. Although it is said that extirpation of nontoxic goiters and adenomas should be without risk, this seems to be a goal more sought after than actually obtained, particularly when applied to all clinics and hospitals.

Single nodules or masses in the thyroid gland are the most frequent site of malignant lesions. This has been particularly emphasized by Lahey.<sup>14</sup> The greatest number of patients studied likewise had a single nodule or mass as the site of the neoplasm. Thus, it seems that many of these single nodules should be removed, particularly in young people, for in a nonendemic area nodules are rare below the age of thirty,<sup>6</sup> and should arouse suspicion of a malignant lesion. On the contrary, it seems unnecessary to remove all multinodular glands because they are infrequently the site of cancer and so prevalent, even in nonendemic areas, that the disadvantages of removal outweigh the advantages.

Some pathologists have considered nodules in the thyroid gland to be "almost physiological," especially in women after the age of fifty.<sup>6</sup>

Certain signs in a gland with one or more nodules, however, are indications for removal of the nodule. They are any increase in size, especially in the absence of thyrotoxicosis, and any suggestion of increased firmness or fixation of the surrounding tissue. The first sign is probably the more important because the other connotes more extensive involvement. Multinodular goiters may well be treated conservatively but deserve careful observation.

Of the patients with malignant neoplasms of the thyroid gland 7.8 per cent had thyrotoxicosis. This figure is slightly higher than that in other reported series.<sup>1, 5, 15</sup> It is still to be noted, however, that cases of malignant neoplasm accompanying thyrotoxicosis are rare, for in 1308 cases of thyrotoxicosis there were 5 patients (0.38 per cent) with malignant neoplasms.

What effect the treatment of thyrotoxicosis with thiouracil will have on thyroid cancer must await future evaluation. Bielschowsky<sup>16</sup> has shown that simultaneous administration of 2-acetyl-amino-fluorine and allyl-thiourea produced adenomas and malignant neoplasms in the thyroid glands of rats, whereas either of these drugs used alone did not produce the neoplastic lesions. We have administered 2-acetyl-amino-fluorene and thiouracil simultaneously to a series of 12 rats, and although malignant tumors of the breast and other organs developed in 8, the only detectable lesion in the glands was hyperplasia. To date, there is no clinical evidence that thiouracil is a predisposing factor or that it has increased the incidence of cancer.

Regarding "prophylactic surgery" for nodular or diffuse goiter in the prevention of thyrotoxicosis, we believe that this complication can be well treated, should it arise, with antithyroid drugs and surgery.

#### SUMMARY

The total number of patients admitted to the Boston City Hospital, the Johns Hopkins Hospital and the Massachusetts General Hospital in periods of twelve, five and eight years, respectively, was 544,918. Among these patients there were 3221 with goiters and 64 with a histologic diagnosis of a malignant neoplasm of the thyroid gland.

The clinical picture and the course of the patients with malignant thyroid neoplasms are discussed, with particular reference to the types of pathological lesions and their degree of malignancy.

It was found that in clinical and autopsy material malignant neoplasms of the thyroid gland were infrequent. The majority of patients dying of malignant lesions had highly malignant tumors that were generally of rapid onset and of short



duration, and in these patients "prophylactic" surgery had rarely been performed

Patients with thyroid tumors of lesser degrees of malignancy do not have a hopeless prognosis. Sometimes, even with apparently widespread metastases, they live for more than ten years.

It is not believed that all nodular goiters should be removed. Despite "prophylactic" surgery on benign or clinically unsuspected malignant goiters, lesions may later develop or frequently recur. Moreover, operations on patients with nontoxic goiter are associated with a significant number of complications and are sometimes fatal.

Single nodules, particularly in young people, should in most cases be removed, and any nodule showing an increase in size, in the absence of thyrotoxicosis, or in firmness or fixation should be extirpated.

We are indebted to Drs. James Means, Oliver Cope and Benjamin Castleman, of the Massachusetts General Hospital, and to Dr. Alfred Blalock, of the Johns Hopkins Hospital, for permission to study the case records at those hospitals.

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## USE OF PENICILLIN IN THE TREATMENT OF CARRIERS OF BETA-HEMOLYTIC STREPTOCOCCI AMONG PATIENTS WITH RHEUMATIC FEVER

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THE danger of hemolytic streptococcus respiratory infection to persons who are susceptible to rheumatic fever is well recognized. Since with present knowledge there are inherent difficulties in evaluating the innocuousness of a given strain, every carrier of beta-hemolytic streptococci must be considered a potential menace to a population of rheumatic-fever patients. Prolonged isolation of such carriers is inadvisable from the psychologic standpoint and is usually impracticable. Hence, means of abolishing the carrier state are desirable.

During the administration of sulfonamides to carriers the throat cultures become negative for hemolytic streptococci in some cases, whereas in others the cultures, although remaining positive, usually yield only small numbers of the organism. In most cases, however, when therapy has been discontinued, nose or throat cultures again become strongly positive.<sup>1-11</sup>

Many investigators have found penicillin to be a more effective agent than sulfonamides for the treatment of hemolytic streptococcus respiratory infections. From these reports it also seems that during penicillin therapy hemolytic streptococci disappear from the nose and throat in nearly all cases. After the discontinuation of treatment the organisms have reappeared in a varying proportion of the reported cases, depending apparently on the dose of penicillin and the number of days of treatment.<sup>7-18</sup>

With a view to preventing the spread of hemolytic streptococci from one patient to another, since November, 1945, penicillin has been administered to all patients at the House of the Good Samaritan found to have positive throat cultures. The following brief extracts of cases observed at the hospital in the early autumn of 1945 illustrate the need for the elimination of beta-hemolytic streptococci from the upper respiratory tract of carriers.

CASE 1. W. J., a 5-year-old boy with rheumatic heart disease and subsiding rheumatic fever, had been a patient at the House of the Good Samaritan since July, 1945—an interval of four months. Fifteen of the twenty-one cultures of the throat taken from August 1 to November 7 yielded Group A beta-hemolytic streptococci, Type 30. The child had large tonsils and cervical adenopathy. Twice during September and October he developed a profuse purulent nasal discharge, which also yielded beta-hemolytic strepto-

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cocci on culture, although there were no elevation of temperature and no other associated signs of illness. The serologic type of the isolated streptococci did not change.

On October 1 another small boy (Case 2) was admitted with the diagnosis of rheumatic fever, rheumatic heart disease and chorea. Three successive daily routine admission cultures and subsequent weekly ones were negative for hemolytic streptococci until October 25, when the patient was moved into a large ward in which the only other occupant was the patient discussed above. The distance between the beds was about 20 feet, and neither child was permitted out of bed. Cultures of the throat in Case 2, taken on October 29 and 30, were positive (1+ and 4+,\* respectively) for

The other girl, M. S., was admitted late in August, looked well and had no signs or symptoms of rheumatic fever except for a subcutaneous nodule and intermittent elevation of the erythrocyte sedimentation rate. The throat cultures contained no hemolytic streptococci. In early October J. R. was allowed out of bed for brief intervals with resulting direct contact with her wardmates, one of whom, M. S. developed throat cultures lightly positive for hemolytic streptococci, Type 28, with no signs or symptoms of acute streptococcal infection and with notable absence of fever. Within 2 weeks of the date of the first positive culture however erythema marginatum appeared and was followed by significant elevations in the antistreptolysin O titer and sedimentation

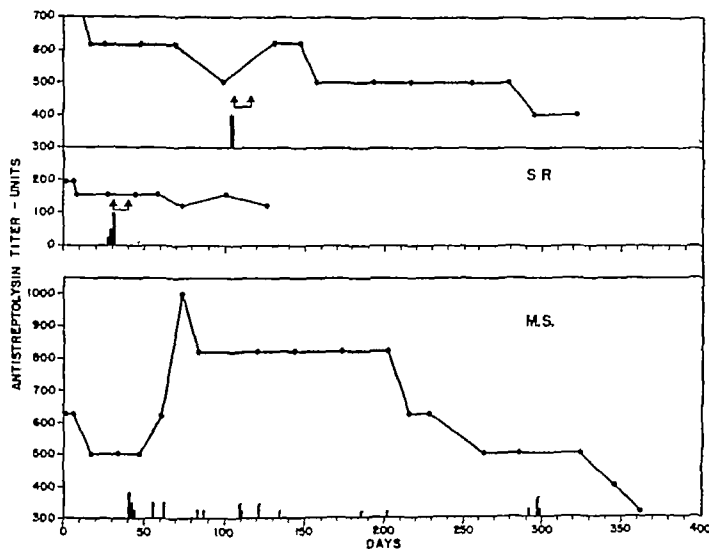


FIGURE 1 Antistreptolysin Titers

The black columns represent positive throat cultures the height of the column corresponding to the heaviness of the growth. The intervals of penicillin therapy are indicated by the arrows.

Group A beta hemolytic streptococci Type 30 and on October 31 this child developed severe tonsillitis, with a maximum temperature of 105°F. Penicillin treatment was initiated within 4 hours of the onset of the clinical illness and continued in dosages of 10 000 units every 2 hours, being given intramuscularly for 10 days to a total of 1 200 000 units. A culture taken 18 hours after the beginning of the therapy as well as all subsequent ones, contained no beta hemolytic streptococci. The acute illness subsided promptly and no recrudescence of rheumatic fever occurred. The other occupant of the room received penicillin in the same dosage for the same length of time and although the culture became negative for hemolytic streptococci, the lymphadenopathy and tonsillar hypertrophy persisted.

CASE 3. J. R. one of two 7 year-old girls who occupied adjacent beds in a large ward, had been a carrier of beta hemolytic streptococci Type 28, as well as, occasionally a second untypable (X) strain, during the 7 months since admission in April, 1945. Of 43 throat cultures taken during that time, 38 were recorded as 1+ to 4+ with Type 28 predominating.

\*Grades 1+ to 4+ represent increasing heaviness of growth of organisms on culture plates.

rate and by the development of many nodules, mild arthralgia, transient tendon contractures, hepatitis, later chorea and auscultatory and electrocardiographic evidence of heart disease including pericarditis. The rheumatic syndrome persisted for months during which the streptococci occasionally reappeared in the throat cultures (Fig 1).

It is apparent that in these 2 cases hemolytic streptococci were transmitted from a chronic carrier to a susceptible person. In 1 case the streptococcal invasion caused a severe clinical respiratory infection, which, however, was not followed by a recurrence of rheumatic fever. In the other case the resulting streptococcal infection, although subclinical, precipitated a recrudescence of rheumatic fever.

#### PROCEDURE

All patients whose routine throat cultures yielded hemolytic streptococci were followed by means of

cultures taken at least three times a week until the presence of the carrier state was established — that is, until the number of positive cultures was shown to be well in excess of the number of negative cultures, with no tendency to diminish

Any patient suffering from an acute streptococcal infection was placed under treatment with penicillin as soon as the diagnosis was made. A control culture was taken just before the first dose of penicillin. In such cases the treatment was identical with that given the healthy carriers.

Penicillin — in doses of 10,000 units every two hours, day and night, for ten days — was given in-

were given penicillin prophylactically, beginning immediately after operation and continuing until the operative wound was healed and there was no fever.

## RESULTS

The primary object of the experiment was achieved in most cases — that is, beta-hemolytic streptococci were eliminated from the throat cultures in 17 of 20 cases for the duration of the post-treatment observation periods, which ranged from twenty\* to one hundred and forty-six days (Table 1). Of the seventeen organisms that yielded to treat-

TABLE 1 *Effect of Penicillin Therapy\**

CASE No	HEMOLYTIC STREPTOCOCCUS	SENSI- TIVITY OF ORGAN- ISM†	PRETREATMENT CULTURES				POST-TREATMENT CULTURES				POST-TONSILLECTOMY CULTURES			
			GROUP	TYPE	UNIT/CC	INTER- NAL days	NO TAKEN	NO POSITIVE	GRADE	INTER- NAL days	NO TAKEN	NO POSITIVE	GRADE	THROAT
1	A	30	01	99	21	15	0-4+	125	33	0		Negative	Negative	Negative
2	A	30	006	3	3	3	1+-4+	102	40	0		—	—	—
3	A	28X	008	190	43	38	0-4+	96	31	0		—	—	—
4	A	12	02	2	2	2	4+	180	28	0		Negative	Negative	Negative
5	A	1	02	24	14	12	0-3+	20	11	0		—	—	—
6	A	X	008	23	20	16	0-3+	77	15	2	1+	—	—	—
7	A	5	01	30	15	14	0-3+	185	43	0		Negative	Negative	Negative
8	A	X	01	123	37	21	0-2+	150	32	0		Negative	Negative	Negative
9	A	X	04	158	53	17	0-2+	35	7	0		—	—	—
10†	A	5	04	13	9	5	0-2+	140	22	0		—	—	—
11†	A	5	04	16	11	11	1+-4+	190	30	0		—	—	—
12	Unknown (not A, C or H)	19	06	21	11	10	0-3+	29	10	7	1+-2+	—	—	—
13	A	02	12	6	6	6	1+-3+	125	17	0		—	—	—
14	Unknown (not A, C or H)	006	23	12	7	7	0-2+	54	12	0		—	—	—
15	A	02	22	12	8	8	0-1+	51	20	0		—	—	—
16	A	30	02	14	8	5	0-2+	165	27	0		—	—	—
17	Unknown (not A, C or H)	14	14	8	6	6	0-1+	24	9	5	1+	—	—	—
18	Unknown (not A, C or H)	008	62	19	17	17	0-3+	112	30	0		Negative	Negative	Negative
19	A	X	008	16	15	13	0-2+	56	20	0		—	—	—
20	A	X	02	4	4	4	3+-4+	146	22	0		—	—	—

\*Penicillin dosage in each case, 10 000 units every two hours, for ten days to total of 1 200 000

†Minimum inhibiting concentration of penicillin

‡Sisters

tramuscularly to a total of 1,200,000 units to all patients in these two classifications.

The organism isolated in each case was grouped and typed by the Lancefield capillary precipitin technic,<sup>19</sup> and its sensitivity to penicillin determined.

Throat cultures were taken three times weekly during treatment, daily from one to two weeks after treatment and then with gradually decreasing frequency to a routine weekly schedule.

Antistreptolysin O titers and erythrocyte sedimentation rates were followed at bi-monthly intervals.

When tonsillectomy was clinically indicated in the penicillin-treated cases, it was performed after the rheumatic fever had subsided and was preceded by several daily throat cultures, the last immediately before operation. Cultures of the open tonsillar fossae were obtained during operation, and the tonsils were sectioned and cultured. The patients

ment, fifteen belonged to Group A, whereas the extracts of two failed to precipitate with A, C or H serums (Cases 14 and 18). In 2 of the 3 unsuccessful cases (12 and 17) the organisms, not of Group A, were also morphologically atypical and weakly hemolytic, in the third, the organism was an untypable strain of Group A, which was unusually sensitive to penicillin in vitro. There was no known factor common to these three organisms by which they differed from the seventeen that yielded to treatment. In 2 patients (Cases 3 and 5) the cultures became positive a second time, but with organisms of types different from those originally recovered.

The downward trend of the antistreptolysin O titer was apparently unaltered by the treatment of chronic carriers with penicillin. In 2 cases of acute streptococcal infection (Cases 2 and 4), each treated

\*Infection with a new type of streptococcus appeared on the twentieth post-treatment day in 1 case.

within two days of the appearance of the organism in the throat culture and within four hours of the onset of the clinical illness, there was no significant rise in the antistreptolysin titer (Fig. 1) and no recrudescence of rheumatic fever. In contrast, in another patient, M S., who was not treated because the infection was subclinical, the antistreptolysin titer rose from 500 to 1000 units coincident with the development of multiple signs and symptoms of rheumatic fever. These observations suggest that a careful comparative study of penicillin-treated and untreated cases of streptococcal infection in patients with rheumatic fever should be undertaken.

In each of the 2 cases in which an organism was believed to have been transmitted from one patient to another, the streptococcus recovered from the recipient appeared to be more sensitive to penicillin

other, and in each case in which beta-hemolytic streptococci were found in one or both of these cultures, two additional cultures were obtained at intervals of a few days. Treatment was instituted in the 6 cases in which these preliminary cultures were positive.

Penicillin in beeswax and peanut oil was given to each of the selected patients intramuscularly in single daily doses of 150,000 units for ten days, to a total of 1,500,000 units. Throat cultures were taken at intervals of three or four days, beginning twenty-four hours after the first dose of penicillin — that is, just before the administration of the second dose. Serum penicillin concentrations were determined at specific intervals (Table 2).

These observations were necessarily less complete than those on patients in the House of the

TABLE 2 Results of Penicillin Therapy\* in Repeated Streptococcal Infections at Wellesley Convalescent Home

PATIENT	PRE-TREATMENT CULTURE			POST-TREATMENT CULTURES			SERUM PENICILLIN CONCENTRATION		
	NO. TAKEN	NO. POSITIVE	GRADE	NO. TAKEN	NO. POSITIVE	GRADE	AT 2 HR.	AT 10-14 HR.	AT 24 HR.
D	3	3	2+4+	5	0	—	0.2	0.03	0.012
G	3	3	1+4+	5	0	—	—	0.075	<0.012
N	3	3	1+3+	7	0	—	0.015	0.03	<0.012
C	4	3	0+4+	3	0	—	0.3	0.02	<0.012
M	3	3	1+4+	6	2	0-2+	0.2	0.02	0.015
A	3	3	3+4+	3	0	—	0.2	<0.012	—

\*Penicillin in beeswax and peanut oil given intramuscularly in single daily doses of 1,500,000 units for ten days, to total of 1,500,000 units

than that of the carrier donor, although it is acknowledged that the differences are within the limits of error. In 1 case the inhibiting concentration of penicillin in vitro dropped from 01 to 006 units per cubic centimeter, and in the other, from 008 to 006 units on repeated determinations.

Tonsillectomy was performed in 5 of the treated cases. In each of these, cultures of the throat, tonsillar fossae and sectioned tonsils were negative for beta hemolytic streptococci. It may be noted that the intervals between penicillin treatment and operation ranged from one hundred and twenty-five to one hundred and eighty-five days. It would be of importance to determine whether the complete eradication of hemolytic streptococci from the interior of the tonsils and the other deep tissues of the upper respiratory tract by means of penicillin had any influence on the chronicity of rheumatic fever.

#### EXPERIENCE WITH SLOWLY ABSORBABLE PENICILLIN

A program similar to that described above was undertaken at a convalescent home,\* where repeated rounds of streptococcal infections had been troublesome.

Two sets of throat cultures of patients and personnel were obtained within a few days of one an-

Good Samaritan because of the shorter hospitalization periods and the heterogeneous types of cases, as well as the geographical distance of the institution from the laboratory. None of the strains obtained from these patients was classifiable with available typing serums. In 5 cases the cultures remained free of hemolytic streptococci for the duration of the observation period (about one month), in the remaining case the culture again became positive, but whether the organism was of the same or different type could not be determined.

#### SUMMARY

Eighteen chronic carriers of beta-hemolytic streptococci and 2 cases of acute streptococcal tonsillitis were treated with a total of 1,200,000 units of penicillin each, given intramuscularly during ten days.

In 17 cases the infecting organisms were eliminated permanently from the throat cultures. One Group A streptococcus and two that did not belong to Group A, C or H failed to disappear.

In 5 cases in which tonsillectomies were performed one hundred and twenty-five to one hundred and eighty-five days after treatment, the tonsillar fossae and sectioned tonsils were free from hemolytic streptococci.

\*The Wellesley Convalescent Home through the courtesy of Dr. Henry Gallup.

In 2 cases the antistreptolysin O titers did not rise after acute streptococcal infections that were promptly treated with penicillin.

Penicillin injections once daily for ten days in slowly absorbable form were observed to be successful in eliminating the beta-hemolytic streptococcus carrier state in 5 of 6 cases.

The ability to eliminate beta-hemolytic streptococci from the throats of most patients in close contact with persons who have had rheumatic fever suggests a practical method of protecting the latter group from beta-hemolytic streptococcus infection.

It is evident that further observations are needed to ascertain whether prompt penicillin treatment for acute hemolytic streptococcus infections in subjects with rheumatic fever may decrease the likelihood of a recurrence of rheumatic fever.

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## THE VALUE OF THE METHYLENE BLUE TEST IN THE DETECTION OF BILIRUBIN\*

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WHEN Fellingner and Menkes<sup>1</sup> described a modification of Franke's<sup>2</sup> methylene blue test for bile in the urine, they suggested that certain quantitative potentialities of the test existed. They observed that determinations made on twenty-four-hour collections of urine paralleled blood bilirubin levels to a satisfactory degree. Determinations on individual samples, however, were not reliable, since dilution factors, as represented by varying specific gravities of the urine, affected the depth of color that took place after the addition of methylene blue. The depth of color in their technic represented the basis of quantitative interpretation.

Gellis and Stokes,<sup>3</sup> after considerable investigative studies, reported a further modification of the original test. They suggested that it might be used as an aid in the early recognition of bilirubinuria in infectious hepatitis. The authors did not claim to describe an unusually sensitive or accurate test for the presence of bilirubin but rather to suggest that the test could be used for demonstrating bilirubinuria

in working with large numbers of soldiers in the field.

The present investigation was undertaken to determine the accuracy and reliability of the test as judged by civilian medical standards, in an effort to determine whether it has any place in routine laboratory procedures. The technic used was that described by Stokes and Gellis.<sup>3,4</sup> This consisted of a drop by drop addition, to 5 cc of urine, of an aqueous methylene blue solution (0.2 per cent by actual dye content) from a 1-cc pipette delivering 20 drops per cubic centimeter. If 5 or more drops were necessary to change the green color of the mixture of urine and methylene blue to a blue color, the test was considered positive for bilirubinuria.

Investigators at the Boston City Hospital<sup>5</sup> found that chrome pigments other than bilirubin gave a greenish color when methylene blue was added and therefore believed that the test was not specific. Other workers had previously made the same observation.<sup>6,7</sup> Roch,<sup>7</sup> indeed, offered this lack of specificity as a criticism of Franke's original test. Figg's<sup>8</sup> criticism was of a similar nature, and appeared in print shortly after Myers<sup>9</sup> had reported

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that he had adapted the test as an early demonstration of toxic hepatitis resulting from industrial toxins. Recent spectrophotometric studies made by a group at the Mayo Clinic<sup>9, 10</sup> demonstrated that the color changes involved in the test were unquestionably due to a blending of blue and yellow colors, rather than to some specific chemical reaction

urine is not unusually high. As demonstrated below in detail, the deeper color of the more concentrated urines may give a falsely positive reaction with methylene blue.

Studies of urine in patients receiving more than 600,000 units of penicillin in twenty-four hours gave three borderline and one distinctly falsely

TABLE 1 *Penicillin-Containing Urines (from Patients Receiving less than 300,000 Units) in 6-hr. Specimens*

DIAGNOSIS	PENICILLIN DOSEAGE units	SPECIFIC GRAVITY	FOAM TEST	HARRISON TEST	METHYLENE BLUE TEST
Syphilis, primary; Herxheimer reaction*	160,000	1.016	++	±	4
Otitis media; myocardial infarct	160,000	1.006	+	±	1
Bronchopneumonia, diabetes and arterio-sclerotic heart disease, with failure hepatomegaly	90,000	1.011	+	0	3
Diabetes ulcer with cellulitis	200,000	1.015	0	0	1
Empyema and pneumonia	160,000	1.008	0	0	1
Keratodermatitis; cellulitis of legs	160,000	1.016	0	0	1
Syphilis, secondary; chancre	160,000	1.030	±	0	3
Syphilis, primary	160,000	1.027	±	0	2
Osteomyelitis; amyloid disease	300,000	1.010	0	0	1
Bronchopneumonia, diabetes and arterio-sclerotic heart disease with failure hepatomegaly	90,000	1.012	±	0	1
† Gall-bladder disease†	120,000	1.010	+++	+++	11
Diabetic gangrene	120,000	1.007	0	±	1
Carcinoma of sigmoid, with abscess	120,000	1.006	0	±	1
Sprue, hematoma and bleeding tendency	120,000	1.008	0	±	2

\*In this case the patient had just had a moderately severe Herxheimer reaction which might have accounted for the borderline bilirubinuria as shown by the Harrison test.

†In this case the patient was later proved to have an empyema of the gall bladder and undoubtedly had a regurgitant type of jaundice due to edema of the biliary passages.

between methylene blue and bilirubin. In general medical practice there are several chrome pigments that might interfere with the accuracy of the test. Two of these, penicillin and riboflavin, were chosen

positive methylene blue tests. The Harrison and spot diazo tests,<sup>11</sup> however, indicated that these specimens contained no bilirubin. The foam test in these cases was positive and hence misleading.

Studies on 4 patients receiving large amounts of components of the vitamin B complex or moderate amounts of pure riboflavin (3 to 5 mg.) revealed falsely positive tests with methylene blue in 3 cases and a borderline reading in 1. The foam test was positive in all cases. The Harrison and spot diazo

TABLE 2 *Comparison of Methylene Blue Test with Depth of Pigment Color in Urine Containing Penicillin\**

DATE	TIME OF PASSAGE OF SAMPLE	METHYLENE BLUE drops	SPECIFIC GRAVITY	COLORIMETER†	
				G VALUES	L* VALUES
2/18	11:00 a.m.	4	1.015	70*	1503
	12:00 p.m.	2	1.012	77*	1135
2/19	7:30 a.m.	1	1.006	83*	0796
	2:00 p.m.	2	1.012	75*	1235
	4:30 p.m.	1	1.003	87*	0568
2/22	8:00 a.m.	4	1.017	69*	1565

\*Patient received 900,000 units in twenty-four hours.

†Evelyn—440 filter.

for study because of their present popularity as therapeutic agents. Patients receiving these substances were studied in some detail to determine how much of the substances was necessary to cause a yellowish discoloration of the urine sufficient to give a falsely positive test on the addition of methylene blue.

Studies were first made on a group of 14 patients receiving less than 300,000 units of penicillin in twenty-four hours. Urinalyses showed that the methylene blue test may give reliable results (Table 1), so long as the specific gravity of the

TABLE 3 *Representative Samples, Showing Effect of Reaction on Methylene Blue Test*

METHYLENE BLUE	REACTION	METHYLENE BLUE	REACTION
3	pH4	13	pH1
4	pH5	13	pH3
4	pH6	13	pH4.5
4	pH7	13	pH6
4	pH8	15	pH9

tests, however, were negative. It is apparent, therefore, that both riboflavin and penicillin may give falsely positive foam and methylene blue tests.

The effect on the methylene blue test of concentration of chrome pigments in the urine was clearly demonstrated by a study of samples of urine with varying specific gravities from a patient receiving 900,000 units of penicillin daily. The results are recorded in Table 2. Urines with low specific gravities (1.003 to 1.006) required but 1 drop of

methylene blue to complete the appearance of a blue color. Urines with higher specific gravities (1.015 to 1.017) required 4 drops of methylene blue to give a positive test. Accurate comparisons of the depth

Table 3 The changes in reaction were made by the addition of varying amounts of acetic acid and sodium hydroxide to the specimens of urine to be tested. In 1 case urine from a jaundiced patient was

TABLE 4 Comparison of Tests for Bile in the Urine

DILUTION	FOAM TEST	METHYLENE BLUE TEST	HARRISON TEST	SPOT DIAZO TEST	WATSON TEST	NAUMANN MODIFICATION OF SPOT DIAZO TEST	NAUMANN MODIFICATION OF HARRISON TEST	IODINE TEST
1:2	++++	6	++++	+++	++++	—	—	+
1:4	+++	4	+++	++	+++	—	—	+
1:8	++	2	++	+	++	—	—	±
1:16	+	1	+	+	+	—	—	0
1:32	±	1	±	+	±	—	—	0
1:64	0	1	±	+	0	—	—	0
1:128	0	0	0	+	0	+	+	0
1:256	0	0	0	trace	0	+	+	0

of color of these specimens were made with the Evelyn colorimeter using a 440 filter. The range in values obtained paralleled quite closely the range in specific gravities of the specimens. This not only is

tested. In another the tests were made on a specimen of normal urine to which pure bilirubin was added. There was a slight tendency for more methylene blue to be required in the more alkaline

TABLE 5 Penicillin-Containing Urines in Patients Receiving More Than 600,000 Units (6-a.m. Specimens)

DIAGNOSIS	PENICILLIN DOSAGE units	SPECIFIC GRAVITY	FOAM TEST	HARRISON TEST	METHYLENE BLUE TEST
Rheumatic heart disease and subacute bacterial endocarditis	625,000	1.003	0	0	1
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.014	++	0	3
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.008	++	0	4
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.012	++	0	4
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.010	+++	0	6
Rheumatic heart disease and subacute bacterial endocarditis (2 p.m.)	900,000	1.005	0	0	1
Rheumatic heart disease and subacute bacterial endocarditis	900,000	1.014	++	0	4

further corroborative evidence that the methylene blue test depends on a physical blending of pigments but also substantiates the findings of Fellingner

solutions (Table 3), but not enough to be considered a real factor.

To compare the relative sensitivity of the methylene blue and other popular tests for bilirubinuria, determinations of serial dilutions of a specimen of urine from a jaundiced patient were made. The results are recorded in Table 4. The Naumann<sup>12</sup> concentration test is certainly the most sensitive, and may in fact demonstrate the presence of bilirubin in normal urine. The Harrison,<sup>11</sup> the Watson<sup>13</sup> modification of the Harrison and the spot diazo tests,<sup>11</sup> although less sensitive than the Naumann concentration test, are reliable and excellent. The foam test, if carried out under daylight and compared with a control urine, is found to be quite sensitive but also extremely nonspecific, since it will give a falsely positive test in the presence of riboflavin, penicillin and quinacrine (Atabrin). All these tests are considerably more sensitive than the methylene blue procedure.

TABLE 6 Urine\* from Patients Taking Large Doses of Vitamin B Compounds or Relatively Small Amounts of Pure Riboflavin

CASE No.	FOAM TEST	HARRISON TEST	SPOT DIAZO TEST	METHYLENE BLUE TEST
1	++	±	±	5
2	++	0	0	6
3	++	0	0	5
4	++	0	0	4

\*Representative samples of urine tested one to four hours after oral administration of riboflavin.

and Menkes,<sup>1</sup> who demonstrated the influence of specific gravity on the methylene blue test. The effect of the reaction on the methylene blue test was studied, and the results are reported in

There are three approaches to the problem of determining the actual concentration of bilirubin that must be present for the methylene blue test to be positive. One is to add various known amounts of bilirubin\* to urine. Another is to make serial dilutions of urine from a jaundiced patient and to determine the amount of bilirubin present in the greatest dilution giving a positive test. A third method is to determine the total bilirubin content of serum from a jaundiced patient and to determine how much of this serum must be added to measured amounts of urine to give a positive test. It is not the purpose of the present paper to discuss the relative merits or disadvantages of these methods, difficulties and uncertainties are encountered in all of them. Exact quantitative recoveries could not be made when known amounts of bilirubin were added to specimens of urine, regardless of whether bilirubin was added as an alkaline solution, as alkaline chloroform solution<sup>14</sup> or as solution prepared in accordance with the more complicated technic of Grotepass and van den Bergh.<sup>15</sup> The methods for determining the bilirubin content of urines from jaundiced patients were likewise unsatisfactory. Consistent results could not be obtained with Hunter's<sup>16</sup> technic or Godfried's<sup>11</sup> modification of it. In the present study a modification of Godfried's technic was devised so that the final result could be determined by the Evelyn colorimeter, but this also proved disappointing. The third method, although it also has certain drawbacks, gave the most satisfactory and consistent results. The methylene blue test, by the use of this method, was positive when 2 or 3 mg per 100 cc (average of 2.5 mg per 100 cc) of bilirubin was present.

Although the methylene blue test is neither specific nor sensitive, it is of definite value in giving a roughly quantitative index of the daily trend of icterus in a jaundiced patient. It obviates the necessity of multiple venipunctures, which are required for blood bilirubin determinations. It is the only test to date for bilirubin that can be quantitated in unit measures—that is, in drops. The recently described semiquantitative test of Watson and Hawkinson,<sup>17</sup> using their modification of the Harrison spot test and a standard color chart, is not so quantitative as the methylene blue test. Daily variations in the methylene blue test can be kept at a minimum by testing prebreakfast specimens (Table 5). In this manner, changes in the specific gravity will not be great. More accurate determinations may be made on twenty-four-hour collections, provided that the urine is kept in a cool, dark place, preferably in a receptacle whose bottom is covered with a thin layer of mineral oil. Penicillin and riboflavin will not interfere with the

daily determinations of bilirubinuria by the methylene blue test, since in most cases the patient will receive a constant dose of these drugs and excrete a constant amount from day to day (Table 6). The procedure is therefore considered to be of definite value.

## SUMMARY

Evaluation of the methylene blue test for bilirubinuria has yielded the following results. The test is nonspecific and may give falsely positive results when the urine contains yellow pigments, such as penicillin and riboflavin. The test is not significantly affected by changes in the urinary reaction, but is affected by changes in the specific gravity. The test is less sensitive than the Naumann concentration test, the Harrison, the spot diazo and the Watson modification of the Harrison and the foam tests. The Naumann concentration test, however, may give positive results in normal urines, and the foam test is highly nonspecific. The present study suggests that the methylene blue test is positive when the concentration of bilirubin in the urine is 2 or 3 mg per 100 cc. or more. Although the test is neither highly accurate nor specific, it provides a valuable means for estimating the daily excretion of bilirubin in the urine of jaundiced patients.

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\*Eastman Kodak preparation used in present study



## MEDICAL PROGRESS

### GENERAL PRINCIPLES OF THE LABORATORY DIAGNOSIS OF VIRAL INFECTIONS\*

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**VIRUSES** may be defined as ultramicroscopic agents, usually filterable, that are unable to propagate themselves in the absence of living cells and that are frequently the cause of clinical disease in man. This definition does not set off viruses sharply from certain bacteria, in fact, the current view is that "viruses represent the degenerate descendants of larger pathogenic micro-organisms."<sup>1</sup> Laboratory procedures for the specific diagnosis of disease due to bacterial agents are well known and standardized, and can usually be handled satisfactorily by the average hospital laboratory. The identification of virus agents, which is carried out along the same general lines, is rendered difficult by certain characteristics of these agents. The more important of these properties are as follows:

Virus agents range in size from approximately 10 (as in foot and mouth disease and poliomyelitis) to 250 millimicrons or more in diameter (as in psittacosis). Although a few of the larger viruses may be seen with the ordinary microscope, the great majority are too small for its resolving powers. Typical morphology, staining reactions and so forth, which are important in diagnostic bacteriology, are not yet available for the recognition of most viruses.

Virus agents are obligate intracellular parasites, and multiplication does not take place in the absence of living cells. Thus, for their propagation, recourse must be had to tissue culture, animal inoculation or the use of the developing chick embryo. These methods are complicated, expensive and protracted compared to those available for the culture of bacterial agents.

Although, broadly speaking, the resistance of viruses to various chemical and physical forces parallels that shown by the vegetative forms of the majority of pathogenic bacteria, it is characteristic of many of the former agents that their extracellular survival time is relatively brief except under special conditions. For example, cultures of many pathogenic bacteria retain their viability for long periods under varying conditions of temperature if inoculated on agar slants protected from the effects of evaporation. Such a technic permits the shipping of pathogenic cultures from all parts of the world to central laboratories for identification. Unfortun-

nately, no such easy method is available in the identification of virus agents. To maintain their viability in the absence of actively proliferating tissue cells, one must resort to freezing at  $-70^{\circ}\text{C}$  or lyophilization or, less satisfactorily, preservation in 50 per cent glycerol. This makes the problem of transporting or shipping virus agents for any distance a difficult one. This question is discussed in greater detail below.

#### DIAGNOSTIC PROCEDURES

Diagnostic procedures for viral infections may be discussed under the following general headings: isolation and identification of the virus itself, serologic demonstration of the formation of specific antibodies against a virus during the clinical course of the disease, pathological demonstration of specific inclusion bodies, and skin tests illustrating the development of altered skin sensitivity to a specific virus or some fraction of it as a result of infection with the specific agent.

Although in a few virus diseases it is at least theoretically possible to make a specific diagnosis by several of these methods, in general, only one procedure is used for routine diagnostic work. In the majority of cases the serologic approach is the most practical one. The disadvantage of this method is that the diagnosis is made in retrospect, rather than in the early stages of the patient's illness.

#### *Isolation of the Virus Agent*

The isolation of the causative virus agent from a patient and its subsequent identification is usually a costly, laborious and prolonged procedure, hardly practical for use by other than the specialized laboratory. Animal inoculation and injection of the developing chick embryo are the two methods generally used. Mice, hamsters, guinea pigs, ferrets, rabbits and monkeys are the animals most frequently employed.

If the material to be inoculated is uncontaminated by bacterial agents (as in blood or spinal fluid), it may be injected directly into the animal or chick embryo. Material such as tissue is washed with sterile water, weighed and cut into small pieces under aseptic conditions. It is ground in a sterile mortar with sterile sand or alundum and enough buffer solution or broth added to form a 20 per cent

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suspension (Physiologic saline solution appears to have a deleterious effect on some viruses) The suspension is centrifuged at a low speed to throw down the coarser particles, and the supernatant fluid is used for injection

In the event that the material to be inoculated is not free of bacterial agents, it must be suitably treated to obtain a bacterium-free inoculum Filtration is effective for this purpose. Berkefeld, Mandler and Seitz filters are often used In each a filter with a pore size sufficiently fine to hold back ordinary bacteria is employed, care must be taken not to reduce the porosity to a point where virus agents of larger sizes would also be held back Other factors as well as particle size are important in determining the filtrability of an agent the amount of positive or negative pressure applied, and the length of time over which it is exerted, the type and reaction of the suspending fluid and the electrical charge of the filter and of the fluid to be filtered. The presence of larger tissue particles in the suspending fluid results in the rapid clogging of the pores, and for this reason the fluid should be cleared first by centrifugation at a moderate speed (3000 to 4000 rpm for thirty to sixty minutes) or by preliminary filtration through filter paper, or by a combination of both methods Even under favorable circumstances, however, filtration results in a drop in virus titer in most cases

Chemicals have been used to some extent in rendering suspensions bacteria free. Ether is occasionally used, particularly in work with the virus of poliomyelitis,<sup>3</sup> which is relatively resistant to the action of this agent. Similarly, Zephiran (a synthetic detergent) has been used for the isolation of bacteriophages<sup>4</sup> and of the influenza virus<sup>5</sup>

Antibiotics, which are frequently employed in conjunction with chemotherapeutic agents such as the sulfonamides, are particularly useful in the inoculation of embryonated egg Hirst<sup>6</sup> developed the technic of amniotic inoculation of unfiltered penicillin-treated throat washings from patients with influenza as a means of isolating the specific virus If streptomycin or sulfadiazine is added as well the results are even better, and this method is fully as sensitive as animal inoculation This work has recently been extended to mumps<sup>7</sup> Nevertheless, animal inoculation continues to be widely used for the primary isolation of virus agents, whereas the chick embryo plays an important role in the propagation of the virus after its adaptation by animal passage

Once isolated, the virus may be identified by the production of specific pathologic lesions in the experimental animal or by appropriate serologic technics—that is, by complement fixation, virus neutralization, precipitation-flocculation or hemagglutination-inhibition tests with specific antisera These tests are considered below in greater detail

### Serologic Diagnosis

Viral infections in man usually stimulate the production of specific antibodies against the invading virus The demonstration of these antibodies by proper serologic technics offers presumptive evidence of past or present infection with the specific agent This evidence is particularly valuable if it can be shown that the antibodies developed during the course of the patient's illness, since such a finding usually offers convincing proof of the causal relation between the clinical disease and the specific virus The basic principle is analogous to that underlying the serologic diagnosis of bacterial infections For both groups of diseases it is frequently impractical to isolate and identify the causative agent, and recourse must be had to diagnosis by the indirect means of demonstrating the appearance or rise in titer of specific antibodies during the course of the infection This is particularly true in cases of viral infections of the central nervous system, as recently emphasized by Rivers,<sup>8</sup> who points out the difficulty of isolating the causative agent from the blood or spinal fluid

As in diseases of bacterial origin, the results obtained from the examination of a single specimen of serum in any given case rarely permit a final diagnosis The demonstration of a significant antibody titer against a specific virus in a single serum specimen simply means that the patient has at some time been infected with that particular agent There is no assurance that the present illness is causally connected with the occurrence of these particular antibodies, since clinical or subclinical infection in the past may well have been the specific stimulation for their production In certain cases, — for example, in mumps, — however, when a high titer of antibody such as is characteristic of persons who have recently recovered from the specific disease is found in a single specimen, it may be regarded as highly suggestive or presumptive evidence of the nature of the infection, although an increase in titer cannot be demonstrated But, as in bacterial infections, to obtain a conclusive serologic diagnosis it is always necessary to demonstrate a significant rise in antibody titer during the course of the disease Thus, at least two specimens of serum should be examined one drawn as soon as possible after the onset of clinical signs and symptoms and the other approximately two or three weeks later Usually, this interval between the drawing of specimens during the acute and convalescent phases is long enough to permit a significant rise in antibody titer to be detected The most important exception is in the demonstration of neutralizing antibodies, these frequently appear later than the others, and if this technic is to be applied a third specimen of serum should be drawn six to eight weeks after the onset of the disease.

Table 1 presents the frequent combinations of reactions with serums drawn during the acute and convalescent phases and the conclusions that one is justified in drawing from them

Serologic reactions for the identification of virus agents present particular technical difficulties in the preparation of the antigens. Since viruses cannot be propagated in the absence of living cells, the preparation of viral antigens free from troublesome tissue components is usually difficult and sometimes impossible. The viral antigen usually consists of an extract of parasitized cells. In setting up a test it is

ability to neutralize the disease-producing quality of the specific virus, as evidenced by the inability of the serum-virus mixture to cause recognizable disease when inoculated into susceptible animals. They are associated with the globulin fraction of serum, the role of complement in this reaction remains uncertain. Mice are the test animals generally used. Although the results of the test on a single specimen of serum occasionally yield presumptive evidence that the disease in question is due to specific virus, it is usually necessary to demonstrate a rise in the neutralizing antibody titer before

TABLE 1 *Combinations of Reactions, with Their Interpretations*

COMBINATION	SERUM DRAWN DURING ACUTE PHASE	SERUM DRAWN DURING CONVALESCENT PHASE	CONCLUSION
1	Negative	Negative	Disease not due to virus tested
2	Negative	Positive	Disease presumably due to virus tested
3	Positive	Positive (significant rise in titer)	Disease presumably due to virus tested
4	Positive	Positive (no significant rise in titer)	1 — contact with the virus tested sometime in past, with no relation to present illness, 2 — first serum drawn too late in course of disease, 3 — second serum drawn too early in course of the disease
5	Not tested	Negative	Disease not due to virus tested
6	Not tested	Positive	Interpretation impossible, unless titer of second specimen is at least as high as that usually found in persons recently recovered from the disease in question, in such cases a presumptive serologic diagnosis may be made on the basis of these suggestive findings.

necessary to include a control consisting of an extract of normal tissue prepared in exactly the same way. If a viral antiserum — prepared by the injection of a suitable animal with tissue cells containing the virus — is employed, the viral antigen used in the actual test should be prepared from infected heterologous cells if possible. These technical difficulties render the serologic diagnosis of viral diseases more complicated and protracted than the process of applying the analogous tests to diseases of bacterial origin.

Four general types of serologic reactions are used for the practical diagnosis of viral infections: virus neutralization, complement fixation, agglutination or flocculation, or both, and hemagglutination inhibition. The first two find wide application in a variety of diseases, but they are relatively expensive and require time. The third, which can be applied only to the largest virus agents, is limited to variola-vaccinia for all practical purposes. At present the fourth is applicable to influenza and perhaps to mumps, the speed and ease with which it can be carried out, however, give it a distinct technical advantage over the others.

**Neutralization tests** Many viral infections stimulate the production of neutralizing antibodies on the part of the host during the course of the illness. These antibodies acquired their name from their

definite diagnosis can be made. Thus, the test must be run simultaneously on two specimens of serum: one drawn as soon as possible after the onset of the illness, and the other drawn four to six weeks later.

The test is usually carried out with a constant amount of virus and varying dilutions of serum, although the reverse — serial dilutions of virus mixed with a constant amount of serum — may be employed, and is particularly useful in the study of neurotropic viruses. Serial dilutions of the serums from the acute and convalescent phases are set up in parallel, and a constant amount of virus is added to each tube. After the incubation of the virus-serum mixtures, susceptible animals are inoculated with samples from each and carefully followed for the development of the experimental disease. In a positive test serum drawn from the convalescent phase shows a significantly enhanced neutralizing or protective effect as compared to that of the acute phase.

This test has been particularly useful in the diagnosis of diseases of the central nervous system due to neurotropic viruses (lymphocytic chorio-meningitis<sup>8</sup> and the various encephalitides<sup>9-12</sup>). With the exception of poliomyelitis the test animal generally employed is the mouse, and the route of inoculation intracerebral, or occasionally intraperitoneal. Survival of a significant number of mice injected with a

serum-virus mixture is evidence of the presence of neutralizing antibodies, since the amount of virus in the mixture is such that if injected alone it would result in the death of all the mice. In poliomyelitis the monkey has been used as the test animal,<sup>14</sup> but the multiplicity of the virus strains that cross react weakly if at all render this test impractical for routine diagnostic work.

This test is often applied in the diagnosis of viral infections caused by agents other than the strictly neurotropic ones. Theiler's<sup>15</sup> discovery that mice are susceptible to the intracerebral inoculation of the virus of yellow fever led to Sawyer's<sup>16</sup> application of the neutralization test in survey work. In influenza the virus-serum mixture is inoculated intranasally into a lightly anesthetized mouse.<sup>17</sup> At the end of seven days surviving mice are sacrificed and autopsied, and the lungs are examined for evidence of pulmonary consolidation. The neutralizing antibody content of antivaccinal<sup>18</sup> and antitherpes<sup>19</sup> sera can be estimated by the inoculation of suitable mixtures of virus and immune serum on to the chorioallantoic membrane of the developing chick embryo and by the observation of the reduction in pox produced as compared to the number that develop after the inoculation of similar mixtures of virus and normal serum.

**Complement-fixation tests** The viral agents causing infectious disease in man generally possess the property of stimulating the production of specific complement-fixing antibodies in the host as a sequel to infection. As such, the formation of these antibodies is entirely analogous to what happens in the course of infectious disease due to bacterial or protozoal agents, and the principles of the methods used for the detection of these antibodies are entirely similar. To establish an unequivocal diagnosis it is essential to prove that antibodies appear or show a significant rise in titer during the course of the infection. Hence at least two specimens of serum from each patient must be examined, one taken as soon as possible after onset, and the other drawn some days later. Since in some diseases the antibody response may occur as early as five days or as late as five weeks after onset, it may be necessary to test three specimens — during the acute phase, one or two weeks after onset and five or six weeks after onset. In a disease such as influenza A or B in which the antibody response is prompt (frequently within a week) and regular the first two specimens usually suffice.

The antigens employed represent the virus agents or their products. The source is frequently infected animal tissue: monkey parotid gland in mumps,<sup>20-22</sup> mouse brain<sup>23</sup> or guinea-pig spleen in lymphocytic choriomeningitis,<sup>24</sup> mouse brain in the various encephalitides,<sup>25-27</sup> mouse lung in influenza,<sup>28-30</sup> yolk sac in lymphogranuloma venereum<sup>31</sup> and psittacosis,<sup>32</sup> amniotic membrane in mumps<sup>33</sup> and allantoic fluid in influenza.<sup>34</sup> In at least three diseases —

lymphocytic choriomeningitis,<sup>35</sup> influenza<sup>36</sup> and vaccinia<sup>37</sup> — soluble antigens capable of fixing complement in the presence of the specific antibodies have been isolated from infected tissues.

It has been pointed out that since viruses cannot be cultivated on lifeless mediums, infected tissues or body fluids must be depended on as sources of antigen. In certain diseases — notably in poliomyelitis — the virus is present in the infected tissue in such a low concentration that it has so far been impossible to obtain a complement-fixing antigen from them. In others it has proved difficult to obtain antigen suspensions that are devoid of significant anticomplementary activity. This drawback is particularly serious in cases in which the concentration of the virus in the tissues is low and the corresponding antigen relatively weak in complement-fixing ability. Under these conditions any anticomplementary activity renders the interpretation of the test difficult at best, and special techniques have been evolved to surmount this difficulty.

Again, since the source of antigen is infected tissue or fluid, it is necessary to include in each test an additional control consisting of normal tissue or fluid prepared in exactly the same way to rule out misleading nonspecific reactions. Parenthetically, it should be pointed out that in the identification of an unknown virus by serologic means a similar control must be included — that is, if the immune serum was obtained from a rabbit, the virus agent must be tested against normal rabbit serum as well.

**Agglutination and flocculation tests** Diagnostic tests employed in agglutination or flocculation techniques are little used in the study of virus diseases with the exception of smallpox. During the course of this disease the patient develops antibodies that agglutinate suspensions of vaccinal elementary bodies.<sup>38</sup> Conversely, if a suspension of ground-up variolous crusts is mixed with antivaccinal rabbit serum, flocculation occurs and thus furnishes a practical method for the diagnosis of doubtful cases of smallpox.<sup>39-40</sup>

**Hemagglutinin-inhibition tests** The virus agents of certain diseases, notably influenza,<sup>41</sup> mumps<sup>42</sup> and vaccinia,<sup>43</sup> have the property of agglutinating the red cells of certain avian and mammalian species to a varying degree. Fowl erythrocytes are most widely used, but in some cases human Type "O" cells or guinea-pig erythrocytes may be substituted. This phenomenon furnishes a convenient method of titrating virus activity, and as such is widely employed in many laboratories, particularly in those in which influenza studies are being carried out. Analogous to what happens in neutralizing or complement-fixing antibodies, the patient with influenza develops antibodies that inhibit the ability of the virus to agglutinate fowl or human erythrocytes. After the hemagglutinating activity of the virus agent has been determined, four minimal

agglutinating doses of the virus are added to increasing dilutions of the serum to be tested, and fowl or other mammalian erythrocytes are added. In this manner the ability of two or more specimens of serum from a suspected case to inhibit hemagglutination may be compared. A significant rise in titer permits one to make a diagnosis of the disease. Here again the finding of inhibitory antibodies in a single specimen of serum gives only the limited information that at some time in the past the patient has been in contact with specific virus, either through clinical or subclinical illness or through vaccination. The finding of a high titer of antibodies against influenza A or B in a group of 10 to 20 persons recently recovered from an epidemic respiratory disease, however, strongly suggests that the outbreak was due to the specific virus. Since the test will distinguish between influenza A and B, it is a valuable tool in the hands of the epidemiologist for identifying the causative agent of an outbreak of influenza.

As has been pointed out, the mumps virus and the vaccinia virus also possess the ability to agglutinate erythrocytes of various mammalian species, and it is possible that the hemagglutination-inhibition reaction will be developed as a helpful diagnostic tool for some cases of the former disease at least.

### *Pathology*

Most virus agents show predilections for certain types of tissue, and by virtue of these special affinities they are frequently classified as neurotropic (rabies, lymphocytic choriomeningitis, poliomyelitis and the various encephalitides), dermatropic (herpes, variola, varicella, vaccinia and the other human and animal poxes), viscerotropic (yellow fever and mumps) or respiratory (influenza A and B and psittacosis). It is not surprising, therefore, that some virus agents may be identified by the typical pathologic lesions that they produce. Furthermore, certain viruses cause characteristic intranuclear or intracytoplasmic structures, called "inclusion bodies," within the cells that they parasitize, which are quite pathognomonic of the causative agent. The best known of these is the intracytoplasmic Negri body,<sup>43</sup> which is pathognomonic for rabies, but many other virus agents produce analogous bodies, such as the Guarnieri bodies<sup>44</sup> of vaccinia and variola (intracytoplasmic) and the intranuclear inclusion bodies characterizing the lesions of herpes febrilis,<sup>45</sup> herpes zoster<sup>45</sup> and varicella.<sup>46</sup> These inclusion bodies have their chief diagnostic value in the examination of material obtained at autopsy—for example, the finding of typical Negri bodies in the nerve cells of the hippocampus of man or dog is pathognomonic of rabies and, in a dog that has bitten a human being, is a definite indication for the administration of rabies vaccine to the latter.

### *Skin Tests*

In at least four diseases of viral origin (lymphogranuloma venereum, mumps, vaccinia and influenza), it is possible to demonstrate the development of altered skin sensitivity to the virus agent—or some product of it. In the first disease the Frei test consists in the injection of pus from a bubo,<sup>47</sup> of infected mouse-brain suspension<sup>48</sup> or of yolk sac material from infected chick embryo.<sup>41</sup> A positive test is evidenced by the development of an infiltrated inflammatory area with a small, well defined papula. In the Enders test for mumps the material used is a suspension of infected monkey parotid gland<sup>22</sup> or infected material from the chick embryo.<sup>49, 50</sup> As in lymphogranuloma inguinale the reaction reaches its height in forty-eight hours, under proper conditions it fails to show definite necrosis. Since a positive reaction may be due to past as well as present infection, a diagnosis of existing clinical disease cannot be made on the results of the test alone but must be interpreted in the light of the clinical picture. The skin-test materials employed in both these diseases are antigenic and stimulate the production of antibodies that may confuse the serologic picture by causing falsely positive reactions. Hence it is important to complete the serologic diagnostic tests before the patient is tested for dermal hypersensitivity.

It has been shown that infection with influenza A or B viruses results in the development of dermal hypersensitivity to the specific virus or some product of it.<sup>51</sup> As yet no practical use has been made of this test for routine diagnostic work. The so-called "immune reaction" to vaccination with cowpox virus,<sup>52</sup> which occurs in persons who have suffered from smallpox or who have previously been vaccinated, is another example of dermal allergy resulting from infection with a virus agent.

### *COLLECTION OF MATERIAL*

A large number of specimens received by any laboratory doing diagnostic work are apt to be unsatisfactory for testing for the possible presence of viruses because of the failure to realize that these agents are delicate organisms that quickly die out except under special conditions. Similarly, many serologic specimens sent in arrive contaminated or hemolyzed, or both, their value being thereby appreciably decreased. The proper collection and shipping of these materials is essential. An appreciation of some of the more important of these points will permit the laboratory to render far more assistance to the physician.

### *Specimens for the Isolation of Virus Agent*

These usually consist of blood, spinal fluid, pharyngeal or nasopharyngeal washings or tissue. Unless the specimens can be brought to the laboratory within a matter of minutes special treat-

ment to ensure the viability of the suspected virus agent is necessary. Freezing is the easiest and generally the most practicable method of preserving these agents, and the use of dry ice (solid carbon dioxide) facilitates this process. Blood in amounts of at least 10 to 15 cc should be withdrawn with a dry, sterile syringe and placed in the refrigerator. As soon as clotting has taken place the specimen should be centrifuged, and the serum withdrawn aseptically and stored in sterile pyrex Wassermann tubes or vaccine bottles. The pyrex tubes should be sealed with an oxygen flame, and the bottles with rubber stoppers and pull-on aprons. Spinal fluid should be obtained with sterile precautions and similarly stored. For throat and nasopharyngeal washings it is customary to use nutrient broth or buffered isotonic sodium chloride, sometimes fortified with 10 per cent normal rabbit serum. These washings may be spun slowly for a few minutes to throw down the grosser particles, and the supernatant drawn off and stored in proper tubes or vials.

Freezing the contents of the bottles and vials is accomplished by immersing the tubes or vials in a mixture of alcohol and dry ice and rotating them during freezing to reduce the chance of breaking due to expansion of the fluid. The tubes or vials should be carefully wrapped in cotton wool and paper to prevent breakage and packed in a vacuum bottle surrounded by pieces of dry ice. If the tubes or vials are not properly wrapped they are apt to be cracked in transit. Enough dry ice must be put in to keep the material frozen during the period of shipping to the laboratory, which should be reduced to a minimum.

Samples of tissue submitted for virus studies should preferably be placed in wide-mouthed sterile bottles sealed with a rubber stopper held in place by adhesive tape. The material may then be frozen as outlined above and shipped to the laboratory packed in dry ice. Tight stoppering of the tube or bottle is necessary to prevent the ingress of carbon dioxide, since the acid reaction produced by this gas may inactivate the virus agent. If this is not possible, the second method of choice is to ship the tissue blocks in sterile containers filled with sterile 50 per cent neutral glycerol to a level where the tissue is completely submerged. If the possibility of delay in shipping the specimen exists and it is not feasible to maintain the supply of dry ice in the vacuum bottle the second method is the one of choice.

Although it is possible to preserve virus agents in the dried state by the use of the lyophilization apparatus, such a procedure is rarely necessary or practical under the conditions governing the clinician.

#### Specimens for Serologic Tests

Specimens of blood for neutralization, complement-fixation, flocculation and hemagglutination-

inhibition tests should not be frozen. A generous sample of blood (at least 15 cc, if possible), should be withdrawn under sterile conditions, a dry syringe being used. After clotting and centrifugation the serum should be removed aseptically and shipped in a suitable sterile rubber-stoppered tube. It is best to store the specimen from the acute phase in the refrigerator at 4°C until the sample from the convalescent phase is obtained. Both tubes should then be shipped together. Although refrigeration in transit is not necessary the specimens should be protected if possible from high temperatures and should be shipped to the laboratory by the most expeditious route.

All specimens should be suitably labeled so as to ensure their proper identification, and a brief abstract of the clinical history should accompany them.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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### CASE 33421

#### PRESENTATION OF CASE

**First admission** A sixty-three-year-old typewriter mechanic entered the hospital complaining of shortness of breath.

He had been in good health until three years before admission, when he developed a cold with considerable cough productive of heavy brownish sputum. He was placed on digitalis and bed rest for eight weeks. He returned to work and had no further difficulty for two years except for shortness of breath on climbing stairs. During the year prior to entry he had several attacks of nocturnal dyspnea with cyanosis. There had been no pain in the chest or swelling of the ankles. A heart murmur had been discovered at the age of twenty years during an ex-

amination for life insurance. Twenty years later, the patient had a severe attack of arthritis involving the shoulders most severely. There had been no arthritis or rheumatism before or after this episode. At the age of forty-seven years an elevated blood pressure was noted for the first time.

Physical examination revealed a well developed and well nourished man in mild respiratory distress with rapid respirations. The fundi showed slight arteriovenous nicking. The heart was enlarged on percussion. The rhythm was grossly irregular. Basal systolic and diastolic murmurs were heard. A high-pitched to-and-fro sound was noted at the apex and over the aortic area. Crackling rales were present at both bases. The liver was palpable three fingerbreadths below the costal margin.

The temperature was 97°F, the pulse 72, and the blood pressure 170 systolic, 94 diastolic.

Examination of the blood revealed a hemoglobin of 12.2 gm and a white-cell count of 11,300, with 83 per cent neutrophils. The nonprotein nitrogen was 29 mg per 100 cc. The urine had a specific gravity of 1.019 and gave a + test for albumin and a 0 test for sugar.

X-ray examination of the chest showed the heart to be generally enlarged, measuring 18 cm in total diameter (internal chest diameter, 31.2 cm). A film taken in the right oblique position disclosed a localized enlargement of the left auricle and the left ventricle displacing the esophagus posteriorly. The hilar shadows were prominent, with increased

vascular shadows throughout both lung fields. A small quantity of fluid was thought to be present in the left pleural cavity. Under fluoroscopy it was noted that the ventricular pulsations were totally irregular in rate, rhythm and amplitude.

The patient was placed on a low-sodium diet and given digitalis, ammonium chloride and Mercupurin, he quickly improved except for intermittent Cheyne-Stokes respirations. By the time of discharge two weeks later he had lost 10 pounds, and the respiratory symptoms had subsided completely.

*Final admission* (six months later). At home the patient did well for three months on a low-sodium diet with ammonium chloride and digitalis. He then noted the onset of polyuria and polydipsia and lost 12 pounds over a three-week period despite an adequate intake. Examination of the urine revealed a brick-red sugar test. The blood sugar was 441 mg per 100 cc. The patient was given 20 units of protamine-zinc insulin daily and was well controlled thereafter, with blue and occasional green tests. During the six weeks before admission the attacks of breathlessness returned. These were at first relieved by the administration of a mercurial diuretic. Finally, a dry, persistent cough and a return of Cheyne-Stokes respirations were noted. In addition, the patient complained of a plugged sensation in both ears and a feeling of fullness in the epigastrium.

On admission the patient was severely orthopneic. The neck veins were distended in the sitting position. The left border of cardiac dullness was 11 cm from the midsternal line. The rhythm was absolutely irregular, with a rate of 90. Grade III aortic systolic and diastolic murmurs were heard, as well as a Grade II apical systolic murmur. An easily heard apical diastolic rumble was noted. Moist rales were present in both lung fields to the level of the scapula on the right and higher on the left. The liver edge was palpable and slightly tender three or four finger-breadths below the costal margin. There was minimal pitting edema of the ankles.

The temperature was 98.8°F, and the blood pressure 178 systolic, 100 diastolic.

Examination of the blood disclosed a hemoglobin of 11.4 gm and a white-cell count of 12,400, with 84 per cent neutrophils. The fasting blood sugar was 84 mg, and the nonprotein nitrogen 45 mg per 100 cc. The urine had a specific gravity of 1.018 and gave a ++ test for albumin and a 0 test for sugar. The sediment contained 1 red cell and 3 white cells per high-power field.

There was no appreciable change in the x-ray appearance of the chest since the previous examination.

The patient was given 0.2 mg of Paralodin daily. On the day following admission 1 cc of Mercuhydrin was given. The urinary output for the next twenty-four hours, however, was only 640 cc. The dyspnea continued. Mercuhydrin injection was repeated, with no diuretic response.

On the seventh hospital day the patient complained of a steady pain in the right lower quadrant with local tenderness. The liver was no more enlarged or tender than on admission. On the same day he was found to be more severely dyspneic, with respirations of 40 to 50 per minute. He was considerably improved with oxygen, morphine and aminophylline. Examination of the legs at that time was negative.

During the next few days the patient became extremely lethargic. The nonprotein nitrogen rose to 110 mg per 100 cc. The urinary output varied between 500 and 1000 cc daily. The breath became frankly uremic. The abdomen was distended, tympanitic and soft. Fluid intake was increased to 3030 cc on the thirteenth hospital day, with an output of 1140 cc. Urinalysis showed specific gravities of 1.016 to 1.020, + to ++ tests for albumin and a 0 test for sugar. The sediment showed up to 5 red cells and 20 white cells per high-power field. Although the nonprotein nitrogen level dropped temporarily, the clinical appearance remained unchanged. On the fifteenth hospital day a leathery pleural friction rub was noted along the right heart border. During the following week the friction rub grew more widespread, being heard in the right anterior portion of the chest and in the axilla. There were flatness and diminished breath sounds in the right lower portion of the chest posteriorly. Occasionally small amounts of rusty sputum were raised. A chest film showed a small amount of fluid on the right, with areas of atelectasis in the right lower lobe decreasing the size. His condition grew gradually worse, and he expired on the twenty-sixth hospital day.

#### DIFFERENTIAL DIAGNOSIS

**DR CONGER WILLIAMS.** This sixty-three-year-old man died a year and a half after the onset of the cardiac symptoms. He apparently died in cardio-renal failure and possibly with complications in addition to uremia, such as pulmonary infection or infarction and even renal infarction, but I think that it is important at this point to decide what was the underlying lesion in the heart.

First of all, I considered the possibility of rheumatic heart disease, in spite of the patient's age. It is not unusual for a man with rheumatic heart disease to survive to the age of sixty and beyond. We know that at twenty years of age he was turned down for life insurance because of the discovery of cardiac murmurs. This may have been significant at least, it is suggestive. At the age of forty-seven there was some evidence of arthritis. The episode is not described in detail, but it may have represented an exacerbation of rheumatic fever. Another point in keeping with rheumatic heart disease is the description of the murmurs. I take it, from what I read of the murmurs, that the patient had aortic stenosis and regurgitation. But he might have had



mitral stenosis as well, although the diastolic rumble was not heard at the time of the first admission. This does not mean that it was not present. There may have been other factors, such as congestive heart failure, that made it difficult to hear the murmur at that time. Another finding that is at least consistent with mitral stenosis, although not diagnostic, is auricular fibrillation. With the onset of auricular fibrillation, the character of a mitral diastolic murmur will change, as a result of disappearance of the presystolic crescendo, leaving a mid-diastolic rumble, such as that described at the time of the second admission. A diastolic rumble, however, is also found in dilatation of the left ventricle without mitral stenosis. So far, I can see nothing that makes me rule out rheumatic heart disease with or without mitral stenosis to explain these findings.

Next, the possibility of syphilis must be considered. The murmur of syphilitic aortic regurgitation is often a to-and-fro murmur, with a fairly loud systolic component. But again, in the case under discussion, the diagnosis of syphilis can only be mentioned. We are given no information about the blood Wassermann or Hinton reaction, nor do we know anything about a past history of syphilis. Certainly, the description of the aortic murmurs is compatible with that of syphilitic aortitis. It is possible that this patient had a combination of syphilitic aortitis and something else. We know that he had hypertension, but I suspect that it played an unimportant role, at least in the heart disease.

Calcereous aortic stenosis is possible but is usually not associated with a diastolic blow. There is a school of thought that holds that calcareous aortic-valve disease is always on a rheumatic basis. That is not a point to be settled now.

Another possible cause of the presence of auricular fibrillation is chronic coronary heart disease. At this age the complication of auricular fibrillation without other heart disease to explain it is fairly common. I doubt that there was previous myocardial infarction, although there is no report of an electrocardiogram.

The possible causes of the terminal uremia should next be considered. Nephrosclerosis is perhaps the most probable cause in this situation. We should think of the possibility of mercurial poisoning because of the fact that the urinary output decreased after two mercurial diuretics. The toxicity of these compounds is increased in connection with a low urinary output following their administration. Although toxic mercurial nephrosis as a result of these diuretic compounds is rather unusual, there have been 2 reported cases. In one described here in conference a year and a half ago, there was a reasonable assumption that the final uremia was based on the use of mercurial diuretics.\*

Another condition that seems to recur quite often in these conferences is that of primary glomerulonephritis, even in older patients. We have no right to make that diagnosis but only to suggest it.

Renal infarction in a patient with auricular fibrillation has already been mentioned. The patient in the case under discussion had uremia resulting from painless renal infarction without hematuria.

I should like to mention another possibility of renal disease—that is, intercapillary glomerulosclerosis. We know that the patient had diabetes and we also know that he had had albumin in the urine for some time before death.

On the basis of these findings, therefore, I favor a diagnosis of rheumatic heart disease with aortic stenosis and regurgitation, mitral stenosis, auricular fibrillation, cardiac enlargement and congestive heart failure complicated by terminal uremia on the basis of nephrosclerosis and, possibly, a pulmonary infection or infarction in addition.

DR EDWARD F BLAND. Needless to say, this case was somewhat of a puzzle. To take the lesser problem first, the patient developed acute diabetes under our observation during the last two or three months. He had severe, extensive valvular heart disease. We thought that it was rheumatic with a hypertensive element, involving principally the aortic valve with stenosis and regurgitation, and like Dr Williams, we were uncertain whether there was mitral disease in addition. Temporarily, he did well on a low-sodium regime. In fact, we were able to discontinue mercurial diuretics for some months prior to the terminal failure. Then, abruptly, he became worse and failed to respond to mercurial diuretics or anything else, with increasing evidence of uremia. We thought that there was infection or infarction somewhere in the body. We could not make a diagnosis of bacterial endocarditis. The cultures were negative, and it did not look like that. We were uncertain about possible rheumatic infection. He was slightly jaundiced,—that does not appear in the record,—but the van den Bergh reaction was 5 mg per 100 cc, as I recall, which made us suspect more strongly infarction somewhere in the body. We wondered about terminal nephritis or terminal infection in the genitourinary tract, but we were unable to prove either. The patient failed to respond, and died in uremia.

DR WILLIAMS. You did not think at the first admission that the to-and-fro sound described was a friction rub and that he had acute rheumatic myocarditis?

DR BLAND. That was on the original admission. The terminal friction rub was of some interest. It was over the whole right lung, and of such intensity that it was easily palpable.

#### CLINICAL DIAGNOSES

Rheumatic and hypertensive heart disease, with aortic regurgitation

\*Case records of the Massachusetts General Hospital (Case 31451) *New Eng J Med* 233:567-570, 1945

Auricular fibrillation and congestive failure  
 Pulmonary infarct  
 Uremia  
 Nephritis?

#### DR WILLIAMS'S DIAGNOSES

Rheumatic heart disease, with aortic stenosis and regurgitation  
 Mitral stenosis?  
 Cardiac enlargement.  
 Congestive heart failure  
 Auricular fibrillation  
 Nephrosclerosis  
 Uremia  
 Pulmonary infarction?

#### ANATOMICAL DIAGNOSES

Calcareous aortic stenosis  
 Hypertrophy and dilatation of heart  
 Thrombosis of right and left auricular appendages  
 Pulmonary emboli and infarction  
 Renal emboli multiple, with infarction

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY Post-mortem examination showed massive renal infarcts. The right kidney, the side where the pain was, had multiple infarcts, which occupied two thirds of the cortex. The left kidney was enlarged and also showed a single infarct. The source of these emboli was, with little doubt, a thrombus in the left auricle. The auricular appendage was still massively filled with thrombus at the time of autopsy. There was also a large thrombus, and the right auricular appendage, which had been the source of pulmonary emboli, and the right lower lobe of the lung were almost completely involved by three separate infarcts that were nearly contiguous. Also, two infarcts were present in the left lower lobe. The valvular disease of the heart consisted of calcareous aortic stenosis with marked interadherence of the commissures. There is nothing that would allow one to be dogmatic regarding whether or not this developed on the basis of a congenital bicuspid valve, but the mitral valve was completely normal. There were no rheumatic stigmas in the myocardium. The friction rub was obviously due to pleuritis, secondary to the pulmonary infarction. There was a fibrinous exudate, 3 mm thick, over the involved area.

DR. BLAND Before we close, would you be willing to discuss the infrequency of hematuria in massive or extensive renal infarction?

DR. MALLORY I was wondering if anyone would comment because this case and the other case discussed today\* had massive renal infarction, but only occasional red cells were found in the urinary sediment.

DR. BLAND We looked repeatedly for hematuria, but at no time were there more than a few red cells in the sediment.

#### CASE 33422

#### PRESENTATION OF CASE

A seven-year-old boy was admitted to the hospital with extreme dyspnea.

About five weeks prior to admission the child began to complain of dyspnea on exertion. Ten days later vomiting, diarrhea and pain in the right upper quadrant developed, and he began to have rapid, grunting respirations. He was admitted to another hospital, where examination revealed myocardial enlargement in all diameters, with a faint systolic murmur at the apex and an enlarged tender liver. The blood pressure was 80 systolic, 60 diastolic. During the hospital stay the temperature remained normal, and the sedimentation rate was not elevated. An electrocardiogram showed marked left-axis deviation, with a slightly prolonged PR interval. Digitalis was administered, with no appreciable effect. The patient was also given mercurial diuretics, with a good output following the first two doses, but no increase was subsequently noted. After about three weeks of hospitalization, with a steady downhill course, he was admitted to this hospital.

There was a history of partial deafness since birth, aggravated by an attack of whooping cough at the age of four years, and also of subsistence on a diet composed largely of "Coca-Cola," "soda" and pastry for several months.

Physical examination disclosed a poorly nourished, cyanotic boy, who was gasping for breath and partially disoriented. The cardiac impulse was in the sixth left interspace in the anterior axillary line. The heart sounds were of poor quality, and a gallop rhythm was present. A pericardial friction rub was heard at the apex. There were a few moist rales at both bases posteriorly, and a questionable pleural friction rub was heard. The liver edge was palpated 4 cm below the right costal margin, and was tender.

The temperature was 95°F, the pulse 120, and the respirations 60. The blood pressure was unobtainable.

Examination of the blood revealed a red-cell count of 4,680,000 and a white-cell count of 4800, with 88 per cent neutrophils. The urine had a specific gravity of 1.020 and contained a moderate trace of albumin, and many casts were observed in the sediment. An electrocardiogram showed a rate of 150, with a PR interval of 0.14 second and some evidence of intraventricular block.

Cedilamid (0.4 mg) and fluids were administered intravenously. The patient followed a rapid downhill course and died about eight hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR. GERTRUD E. REYERSBACH This is a history of myocarditis and congestive failure, and the prob-

\*Case records of the Massachusetts General Hospital (Case 33311) *New Eng J Med* 237:163-167, 1947.

lem is to decide what type of myocardial disease this child had

The most frequent cause of myocarditis in childhood is rheumatic fever. In most cases myocardial involvement in rheumatic fever is accompanied by fever. Severe myocardial disease without involvement of the endocardium, — that is, without valvular lesions, is rare. The patient is reported to have had a faint systolic apical murmur. This description does not fit too well with valvular disease, but the murmur may have been due to cardiac dilatation and a relative mitral insufficiency.

The prolonged PR interval — we do not know how much prolonged — is consistent not only with a diagnosis of rheumatic carditis but also with some other forms of carditis. We do not know whether the electrocardiogram was taken before digitalis was administered. A normal sedimentation rate in the presence of congestive failure is frequent in rheumatic carditis. Failure to respond to digitalis is not rare, but in this case it may have been due to the fact that inadequate doses of digitalis were administered.

The absence of any other signs of rheumatic fever, such as joint pains, nodules, rashes and epistaxis, makes the diagnosis of rheumatic myocarditis unlikely.

We then come to a second group of diseases that may cause myocarditis in this age group — namely, infection. There is no indication that this boy had such a disease as typhoid fever or that he had a septicemia. Diphtheria is known to cause severe myocarditis. No mention is made of a sore throat or a skin lesion that might have been of diphtheritic origin. A prolonged PR interval, intraventricular block and low blood pressure are often seen in diphtheritic myocarditis, but cardiac dilatation is comparatively rare. Furthermore, one would have expected the boy to succumb earlier had he had diphtheritic myocarditis.

Nothing in the history suggests hyperthyroidism or hypothyroidism, nor is there any mention of the ingestion of such poisons as phosphorus, arsenic and chloroform.

We know that myocarditis occurs in acute hemorrhagic nephritis. I think that we can safely discard this diagnosis without further discussion. Also, the diagnosis of chronic nephritis with cardiac failure can be eliminated. True, a urine examination showed albumin and casts, but these findings are not uncommon in congestive failure. I doubt that they were due to mercury poisoning.

It is said that the patient had subsisted on a diet comprised largely of Coca-Cola, soda and pastry for a few months before becoming sick. This indicates that the diet was poor in thiamine. Did the patient have beriberi? We are not told whether any signs of polyneuritis were found or whether the deep reflexes were diminished. A serum protein

determination is not recorded. In beriberi, the blood pressure is usually low, as in this patient. The heart is greatly enlarged, often generally, sometimes the right side more so than the left. The electrocardiogram usually shows low voltage of QRS segments and T waves. A diagnosis can only be made by clinical observation, careful appraisal of the diet and sometimes a clinical trial with thiamine.

Two rare congenital lesions that produce cardiac insufficiency are the cardiac form of glycogen disease and rhabdomyoma of the heart. In both diseases hypertrophic heart-muscle cells containing large vacuolated spaces filled with glycogen are found. Practically all reported cases of rhabdomyoma have been associated with tuberous sclerosis, of which this child showed no signs.

He may have had cardiac glycogen disease, we cannot make the diagnosis positively during life. I do believe that the large liver was not due to glycogen disease but to congestive failure.

Lastly, we come to the group of interstitial myocarditis described by Fiedler.<sup>1</sup> In these cases cardiac enlargement, often with no murmurs, and congestive failure are apparent clinically. These children are usually afebrile and do not respond well to digitalis or diuretics. The disease is more frequently found in smaller children but has been described in a child of the same age as this patient. The clinical picture and course fit well with this disease.

In making a diagnosis, I believe that we must consider seriously three possibilities: beriberi, glycogen disease and interstitial myocarditis. It is unlikely, however, that he had beriberi myocarditis. I am sure that he must have had thiamine before he went on this peculiar diet, and also I should think that he had received thiamine in some form in the other hospital. This type of myocarditis is more frequently seen in infants with a poor dietary history than in older children. I must therefore decide between glycogen disease and interstitial myocarditis, and I shall guess that he had interstitial myocarditis, congestive failure and terminal pericarditis.

DR ALFRED KRANES: Do you think that the electrocardiographic findings are against interstitial myocarditis?

DR REYERSBACH: A little.

#### CLINICAL DIAGNOSIS

Myocarditis

#### DR REYERSBACH'S DIAGNOSES

Interstitial myocarditis

Congestive failure

Terminal pericarditis

#### ANATOMICAL DIAGNOSES

(Beriberi heart disease, probable)

Diffuse fibrosis of myocardium

Hypertrophy and dilatation of heart

Chronic passive congestion

## PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: Post-mortem examination showed primarily a hypertrophied heart weighing 210 gm. All the chambers were dilated and moderately hypertrophied. The pericardium contained fluid but was clear, and there was no evidence of pericarditis. The valves were entirely normal. The ventricular endocardium seemed slightly thickened. The musculature was not grossly abnormal, but when the microscopical sections came through, they presented a very unusual and interesting appearance. In all of a number of blocks there was diffuse fibrosis, with a moderate degree of edema of the interstitial fibrous tissue. There was no inflammatory infiltration, and there were no areas of necrosis or destruction of the cardiac muscle cells. These cells looked hypertrophied, as one would expect from the increased weight of the heart, and showed mild degenerative changes in which the muscle fibers were widely separated from one another by a homogeneous, slightly hyaline material, which I could not identify. A few cells showed hydropic vacuoles. There was no evidence of glycogen storage.

We are therefore presented with a diffuse fibrosis of the myocardium without evidence of present or past destruction of muscle cells or any traces of inflammation. Most types of myocarditis are associated with extensive destruction of muscle cells—for example, that seen in diphtheria. It is conceivable that an interstitial myocarditis such as is seen following sulfadiazine therapy or in typhus fever can result in fibrosis somewhat similar to what

was observed in this case, but I would expect it to be focal rather than diffuse and there is not the least reason for suspecting such etiologic agents in this patient. On the other hand, this appearance has frequently been described in beriberi.<sup>2-4</sup> Although the histologic picture was not specific, the findings were compatible, and that is my first choice of diagnosis. We found nothing else in the rest of the body that was of any significance, except evidence of congestion and cardiac failure.

DR. ALLAN M. BUTLER: In pediatrics we are often puzzled regarding why we do not see more thiamine deficiency because our infants exist on a diet that is very low in thiamine and often have severe bouts of nutritional disturbance. The diet is sometimes high in sugar, and yet we hardly ever see any objective evidence of thiamine deficiency.

DR. MALLORY: In this part of the world almost the only cases of frank beriberi heart disease are seen in chronic alcoholics.

DR. SEDGWICK MEAD: Were there any changes in the peripheral nervous system?

DR. MALLORY: Unfortunately, they were not studied. There was no clinical evidence of neuritis, however.

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groups of private patients, or by surgeons long on speed and short on incisions. But these patients will not drift off into the happy limbo of another man's practice. They have made their prepayments over the years and they will return for amends, the bad news will gather like flies around offal on a hot summer day. The backers of this scheme will come to realize that, although their expenses have been met, they are operating under a deficit — a type of deficit peculiar to medical undertakings.

The definition and control of competence is the central problem of medicine today. It seems wiser to move toward the solution of this problem than to multiply the total number of doctor-patient contacts by legislation.

### A FITTING MEMORIAL

THE published notice of the services for the late Dr. Robert N. Nye contained a request that flowers be omitted but that in their stead donations be sent to the Massachusetts Division of the American Cancer Society. The request met with a remarkable response. In scarcely more than two weeks over \$1600 had been received, none of it obtained by solicitation.

There is a growing sentiment that this sum should be expanded into a real memorial fund, in view of the great interest that Dr. Nye had in the American Cancer Society, and the time and effort that he had given to it in addition to his editorial and other duties.

Any persons who are interested in adding to this fund should send their donations, in Dr. Nye's name, to the American Cancer Society (Massachusetts Division) Inc., 476 Boylston Street, Boston 16.

### MASSACHUSETTS MEDICAL SOCIETY

#### DEATHS

**HAWKINS** — Henry Hawkins, M.D., of Belmont, died on September 4. He was in his seventy-fifth year.

Dr. Hawkins received his degree from University of Pennsylvania School of Medicine in 1902. He was ophthalmologist at the Perkins Institute for the Blind and the School for Crippled Children. He was on the staffs of the Boston City, Cambridge City and Cambridge Emergency hospitals and was a consulting surgeon to the Massachusetts General Hospital. He was a member of the New England Ophthalmological Society and a fellow of the American Medical Association.

His widow and two sisters survive.

**LUCAS** — Julian D. Lucas, M.D., of Brookline, died on June 3. He was in his seventieth year.

Dr. Lucas received his degree from Tufts College Medical School in 1902. He was a former member of the Massachusetts Medical Society.

**MURPHY** — Harold A. Murphy, M.D., of Jamaica Plain, died on September 23. He was in his fifty-sixth year.

Dr. Murphy received his degree from Tufts College Medical School in 1915.

His widow, a son, two brothers and a sister survive.

### APPLICANTS FOR FELLOWSHIP

The following three names were omitted from the list of applicants published in the *Journal* of October 9.

#### ESSEX NORTH DISTRICT

**WEINSTEIN, MAX I.**, 220 Walnut Street, Lawrence.

Middlesex University School of Medicine, 1936. Sponsor N. F. DeCesare, 57 Jackson Street, Lawrence.

Harold R. Kurth, *Secretary*, 57 Jackson Street, Lawrence.

#### MIDDLESEX NORTH DISTRICT

**PELOQUIN, LAVAL U.**, 834 Stevens Street, Lowell.

Georgetown University School of Medicine.

Brendan D. Leahy, *Secretary*, 9 Central Street, Lowell.

#### MIDDLESEX SOUTH DISTRICT

**PAGEL, MAX MANFRIED**, 21 Clark Street, Newton Centre. University of Breslau, 1920. Sponsor B. P. Colcock, 78 Hull Street, Newtonville.

Alexander A. Levi, *Secretary*, 481 Beacon Street, Boston.

### A HUNDRED YEARS AGO

We have ever found it difficult to impress upon females the importance and absolute necessity of remaining for a sufficient length of time after confinement in a horizontal position, and keeping perfectly quiet. We are satisfied that the practise of getting out of bed too soon after confinement is very general in our community and hence it is that such a very large proportion of our female population suffer with prolapsus and procidentia uteri. Sometimes this is attributable to the want of proper precaution on the part of medical advisers, but more frequently it is owing to the folly of patients themselves. On the third or fourth day after parturition, a patient who is "very smart," feels able to sit up in bed, or in an easy chair, and in spite of all that the physician can say, she will, in his absence, sit up for the purpose of changing her clothes, or get out of bed altogether, that it may be made up, and not infrequently walk across the floor, by way of testing her strength. A moment's reflection must convince any one of the impropriety of such conduct. We are satisfied that if due attention were paid to the proper "getting up" after confinement, we would not see so many young and lovely wives, pale and anaemic, and unable to take the least exercise, or even attend to their ordinary household affairs, without the greatest pain — A quarterly

meeting of the Counsellors of the Massachusetts Medical Society was held at the Masonic Temple a few days ago. There have not been so many Counsellors together at an ordinary business meeting within the compass of our recollection. Everything passed satisfactorily until Dr Childs of Pittsfield resolved that *Whereas*, The great object of medical association is the advancement of medical science, and the promotion of harmony and good feeling in the profession, thereby contributing to the best interests of society, and *Whereas* the present organization of the Massachusetts Medical Society does not fully meet these important objects, therefore, *Resolved*, that a change in the organization of the Massachusetts Medical Society is in our opinion deemed both wise and expedient, and that the change consist in making the basis of the State Society, local or county associations. — The whole number of cases treated by the Physicians of the Boston Dispensary during the year ending Sept 30, was 3290. The number of "Bostonians" in this list is stated in the Abstract of Reports as 163, other Americans, 458, Hibernico-Americans, 657, Irish, 1874. Only 150 of the patients are reported as intemperate. — A great variety of beautiful dental work was on exhibition at the late Quincy Hall fair. By ingenious clock machinery, artificial jaws of porcelain teeth were continually opening and closing, as spectators were passing along. — We are gratified to learn that a Professorship of Insanity has been established at one Medical School. The Willoughby University, Columbus, Ohio, has appointed Samuel M Smith, M.D., Professor of Medical Jurisprudence and Insanity. We think there should be a distinct course of lectures on mental maladies, at every medical school. Dr Smith has some practical knowledge of insanity, having been an Assistant Physician at the Ohio Lunatic Asylum for several years. — Died, in Pembroke, Mass., Dr Anthony Collamore, a worthy physician and an honest man. The disease which occasioned this sad bereavement was dilatation of both auricles, and both ventricles of the heart, without hypertrophy. The pericardium was adherent to the heart, and also the diaphragm and mediastinum. Although confident that disease was praying upon his vitals, yet so slight was the uneasiness occasioned by the inflammation that he was scarce ever detained from attending to the duties of his laborious profession. He had been a practitioner of medicine in Pembroke nearly forty years. He was one of those old-fashioned physicians, who never blazon forth their cures as wonderful. Tender and sympathizing, he softened the pillow of the sick, and dropped a tear with relatives bereaved. Well can it be said, that those who knew him best, deplore him most. — Extracted from the *Boston Medical and Surgical Journal*, October, 1847.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### LOCATION OF RESPIRATORS AND HOT PACK MACHINES IN MASSACHUSETTS\*

CITY OR TOWN	LOCATION OF EQUIPMENT	RESPIRATORS	HOT PACK MACHINES
BARNSTABLE COUNTY			
Hyannis	Cape Cod Hospital	1	1
BERKSHIRE COUNTY			
North Adams	North Adams Hospital	1	—
Pittsfield	House of Mercy Hospital	3	5
BRISTOL COUNTY			
Attleboro	Sturdy Memorial Hospital	1	1
Fall River	Fall River General Hospital	1	2
	St. Anne's Hospital	1	—
	Tremont Hospital	—	2
	Union Hospital	2	2
New Bedford	St. Luke's Hospital	2	1
Taunton	Morton Hospital	1	—
ESSEX COUNTY			
Beverly	Beverly Hospital	2	—
Danvers	Hunt Memorial Hospital	1	—
Haverhill	Hale Hospital	1	—
Lawrence	Lawrence General Hospital	2	—
Lynn	Lynn Hospital	1	1
Newburyport	Anna Jacques Hospital	1	1
Peabody	J. B. Thomas Hospital	1	1
Salem	Salem Hospital	3	1
FRANKLIN COUNTY			
Greenfield	Greenfield Isolation Hospital	1	1
HAMPSHIRE COUNTY			
Holyoke	Holyoke Hospital	1	2
Springfield	Health Department Hospital	1	—
HAMPSHIRE COUNTY			
Northampton	Cooley Dickinson Hospital	1 adult 1 infant (1 resuscitator)	1
Ware	Mary Lane Hospital	—	—
MIDDLESEX COUNTY			
Cambridge	Cambridge City Hospital	1 adult 1 infant	—
Everett	Whidden Memorial Hospital	1	—
Frammingham	Cushing General Hospital	1	—
	Frammingham Union Hospital	1	—
Lowell	St. John's Hospital	—	3
Malden	Malden Hospital	1	1
Newton	Newton Wellesley Hospital	—	1
WORFOLK COUNTY			
Quincy	Quincy City Hospital	1 adult 1 infant	1
PLYMOUTH COUNTY			
Brockton	Brockton Hospital	1	—
Middleboro	Lakeville State Sanatorium	2	3
SUFFOLK COUNTY			
Boston	Beth Israel Hospital	2	—
	Boston City Hospital	6	3
	Corney Hospital	1	—
	Children's Hospital	37	10
	Haynes Memorial Hospital	5	4
	Massachusetts General Hospital	6	—
	New England Baptist Hospital	1	—
	Peter Bent Brigham Hospital	3	1
	St. Elizabeth's Hospital	1	—
	St. Mary's Infant Asylum	1	—
	Veterans Administration Hospital (West Roxbury)	1	—
Chelsea	Chelsea Memorial Hospital	1	—
Revere	Revere General Hospital	1	—
Winthrop	Winthrop Community Hospital	1	—
WORCESTER COUNTY			
Fitchburg	Burbank Hospital	1	2
Gardner	Henry Heywood Memorial Hospital	1	—
Worcester	Belmont Hospital	1	—
	Farlan Hospital	(1 resuscitator)	—
	Morial Hospital	1	—
	Worcester City Hospital	3	—

\*List compiled jointly by the Massachusetts Department of Public Health and the National Foundation for Infantile Paralysis.  
\*Patient respirator room.

## MISCELLANY

### ALVARENGA PRIZE

The College of Physicians of Philadelphia awarded the Alvarenga Prize on July 14, 1947, for this year to Dr. Joseph Aronson, of the United States Bureau of Indian Affairs, in recognition of his studies on the evaluation of BCG vaccine in the control of tuberculosis.

The Alvarenga Prize was established by the will of Pedro Francisco daCosta Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians, to be awarded annually by the College of Physicians on each anniversary of the death of the testator, July 14, 1883, for outstanding work.

### NOTES

The following Massachusetts physicians were recently appointed fellows in the American College of Surgeons: Thomas W. Botsford, Brookline, Weston T. Buddington, Boston, John H. Crandon, Boston, William H. Creamer, Fall River, William F. Croskery, Brookline, George F. Emerson, Boston, Francis J. Hanley, Brookline, Edward Harding, Brookline, J. Hartwell Harrison, Boston, Herbert E. Hedberg, Worcester, Donald Hight, Worcester, Stanley O. Hoerr, Boston, Elwood O. Horne, Worcester, Chester W. Howe, Framingham, George Kelemen, Boston, Benjamin deF. Lambert, Lowell, Henry C. Lawson, Fall River, Joseph P. Marnane, Gardner, John B. McKittrick, Boston, Carter R. Rowe, Boston, Morgan Sargent, Quincy, S. Peter Sarris, Lynn, John A. Seth, Boston, Artemas J. Stewart, Lowell, William W. Teahan, Holyoke, Robert S. Thomson, Roslindale, Howard M. Trafton, Dorchester, John B. Vernaglia, Medford, Joshua H. Weeks, New Bedford, Charles A. Wheeler, Leominster, and Hilary F. White, Fall River.

### NORFOLK MEDICAL NEWS

The *Journal* welcomes the reappearance of the *Norfolk Medical News*, after an interval of two years during which it had suspended publication. Appearing first in 1940 and continuing in regular publication until 1945, the *News* appears now in its sixth volume. Distributed to the entire membership of the parent society, the *News*, offering the use of its pages as a general forum, is more than the journal of a single district.

## CORRESPONDENCE

### A PERTINENT SUGGESTION

To the Editor: Well trained physicians in the Commonwealth frequently see many patients who have been treated poorly — both professionally and financially — by other less well trained physicians, the majority of whom are graduates of medical schools unapproved by the Council on Medical Education and Hospitals of the American Medical Association. Furthermore, most of the physicians with inferior training take their patients to private hospitals not approved as Grade A by the Council on Medical Education and Hospitals. In these hospitals the standards are frequently poor, and surgical and medical care leave much to be desired.

The same physicians are not allowed to practice in first-rate hospitals. Moreover, until the recent institution by the Massachusetts Medical Society of refresher courses for physicians who are veterans, and for any other physicians who might wish to attend, little or no encouragement has been given physicians to improve their professional status and ability. If poor medicine, shabby ethics, and dangerously inadequate hospital care are to be prevented in the Commonwealth, all poorly trained physicians must be encouraged to improve their knowledge, and they must also be rewarded for such improvement. How can this be brought about?

It is my opinion that the Massachusetts Medical Society can do a great deal by offering prescribed courses to all physicians to be given throughout the year by the three leading medical schools in the Commonwealth. These courses should be for the express purpose of allowing those who pass the final examinations to qualify for admission to the courtesy staffs of Grade A hospitals.

Naturally, physicians passing the prescribed courses would also have to qualify morally and ethically. But that problem would rest with the Grade A hospitals that chose to admit to their staffs the physicians who had passed the required courses.

Now that recent legislation prohibits graduates of unapproved medical schools from obtaining licenses to practice medicine in Massachusetts, we have at last only to contend with all the physicians — graduates of the same unapproved schools — who already hold such licenses. Of course, unless they were strongly urged to do so, there would be many substandard physicians who would not take the required courses, and who therefore might never enjoy the benefits of caring for their patients in Grade A hospitals. There would be a great many other such physicians, however, now legally practicing medicine in the Commonwealth, who would jump at the chance to improve their knowledge and so to be accepted by approved medical institutions.

By the offering of such concrete encouragement and opportunity by the Massachusetts Medical Society, many of these well meaning, but unhappily poorly trained physicians, would lose the "chip on their shoulders", they would be in instead of out with the majority of their profession, and at the end of a few years the caliber of medical care in the Commonwealth would be greatly enhanced. The number of second rate and third-rate private hospitals would be reduced materially.

It is hoped that the Society will work toward some such goal as I have outlined above.

J. ROBERT LYMAN, M.D.

24 Forest Street  
Wellesley Hills

## BOOK REVIEW

*Diseases of the Basal Ganglia and Subthalamic Nuclei*. By D. Denny-Brown, M.D., Ch.C., Dr. Phil., F.R.C.P. 8<sup>1</sup>/<sub>2</sub> cloth, 74 pp., with one colored plate. New York: Oxford University Press, 1946. \$2.50. Reprinted from the *Oxford Loose-Leaf Medicine*.

This short monograph is issued as a reprint from *Oxford Loose-Leaf Medicine*, Volume VI, in a convenient form for those interested in the subject. The contents appear to be unchanged. There are a separate index and an extensive bibliography. One illustration in color is fairly satisfactory. The review, by a well known authority, is an excellent one, and all physicians seeking knowledge of the diseases of the basal ganglia are referred to this work. The chief clinical syndromes covered are paralysis agitans, postencephalitic Parkinsonism, hepatolenticular degeneration, dystonia, atetosis and Huntington's and other forms of adult chorea. Each disease is discussed from the point of view of definition, symptomatology, pathology and treatment. Although the article is brief and intended for reference by the internist or the general practitioner, the quality of the evaluations and the clearness of the presentation make this short monograph an outstanding contribution.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*La Douleur*. By Dr. Paul Chauchard, directeur adjoint à l'École pratique des hautes Études. 128 pp., 12<sup>o</sup>, paper, with ten illustrations. Paris: Presses universitaires de France, 1947. Forms No. 252 of "Que sais-je?" Le point des connaissances actuelles.

This small popular work on pain is divided into three parts: physiology, pathology, including visceral, neuralgic and central-nervous-system pain, and treatment, including medical and surgical treatment and means for alleviating pain. The material is well organized, and the text well written. The catalogue of this popular series shows that the whole field of knowledge is well covered. The series should prove interesting to French-reading persons.

*Annual Report of the Baruch Committee on Physical Medicine for the period of April 1, 1945, to December 31, 1946* 8 paper, 161 pp. with 35 illustrations. New York The Committee, 1947 Free.

This is a comprehensive report of the activities carried on by thirteen medical schools supported by grants from the Baruch Committee. The total disbursement for the period under consideration was slightly over \$107,369.

*The Role of Hormones in Sterility* By Bent C. Böving A B 4 paper 38 pp. with one plate (The Schering award for 1946.) Bloomfield New Jersey Schering Corporation Medical Department, 1947 Free.

This essay received first prize in a competition participated in by forty-eight contestants. Mr. Böving is now in the class of 1948 at the Jefferson Medical College. He discusses the various aspects of his subject, especially from the viewpoints of chemistry and physiology.

*Copper and Health*. Issued by the Copper and Brass Research Association 8<sup>1</sup>/<sub>2</sub> paper 47 pp. New York The Association, 1947 Free.

In this pamphlet the various aspects of copper in relation to health are discussed including toxicity value as a nutrient and use in cooking utensils, in water supply systems and in ancient and modern medicine. Much of the information presented in the booklet was compiled by Dr. R. R. Sayers, director of the Bureau of Mines, Department of the Interior when he was serving as chief of the Division of Industrial Hygiene, United States Public Health Service. He was assisted by Sara J. Davenport. The printing is well done with a good type on good paper. This small pamphlet should prove useful for reference purposes in all medical and general libraries.

*Röntgen Interpretation* By George W. Holmes, M.D., member, Board of Consultation, Massachusetts General Hospital, and clinical professor of roentgenology emeritus Harvard Medical School and Laurence L. Robbins, M.D., radiologist-in-chief, Massachusetts General Hospital and associate in radiology Harvard Medical School. Seventh edition, thoroughly revised 8, cloth, 398 pp. with 266 illustrations. Philadelphia Lea and Febiger, 1947 \$7.00.

This standard textbook has been thoroughly revised to include the advances in the subject since the publication of the previous edition including particularly new material on diagnosis and treatment. The book is well published in every way. It should be in all medical libraries and in the libraries of physicians interested in radiologic diagnosis.

*Recent Trends in Alcoholism and in Alcohol Consumption* By E. M. Jellinek, Sc.D. director Section of Studies on Alcohol Laboratory of Applied Physiology Yale University 4<sup>1</sup>/<sub>2</sub> paper, 42 pp. with four figures and twenty-seven tables. New Haven Hillhouse Press, 1947 50 cents.

This is a statistical study of the apparent consumption of alcoholic beverages for the period 1850 to 1945. The first part analyzes the over all consumption for the United States and the second that by states. Population and consumption of persons over drinking age, which is placed at fifteen years are compared.

Separate tables are given for consumption of distilled spirits (liquor) and wine and for total absolute alcohol contained in liquor, beer and wine. Chronic alcoholism is portrayed in a number of tables. The study was projected for the purpose of ascertaining the truth concerning the prevalent opinion that there has been an increase in drinking and a rise of alcoholism particularly among women. The summary reveals that the per capita consumption of alcoholic beverages by persons of drinking age rose steadily during the course of World War II but remained below the levels of the pre-Prohibition years, and that the rise in consumption between 1940 and 1945, as shown by the tables, "was due to an increase of 35 per cent in the number of consumers, but individual consumption hardly increased if at all." Since 1850 the per capita consumption of distilled spirits has decreased by 53 per cent, whereas that of beer has increased by 862 per cent. The estimated number of chronic alcoholics

was greatest in 1910. Between 1915 and 1920 the level dropped sharply and the decrease was maintained during the Prohibition era. Between 1930 and 1945 the rate increased by nearly 28 per cent, but this rate was still 31 per cent below that in 1910.

The rate of female alcoholism was higher in 1910 than in 1945. The drop from 1915 to the Prohibition years was less in the female than in the male rate. Likewise the rise of the female rate between the last Prohibition years and 1945 was only 12.6 per cent as compared with an increase of the male rate of alcoholism of 43.6 per cent. The entire rise in the female rate occurred during the war years. From 1940 to 1945 the female rate increased by 12.6 per cent and the male rate by 22.6 per cent. Dr. Jellinek concludes that there is no basis for the contention that female inebriety is increasing faster than male inebriety. The rate of chronic alcoholism in cities of 100,000 and over is higher by 33.7 per cent than that in smaller cities and higher by 105 per cent than that in rural areas. The entire increase in the rate of chronic alcoholism since 1930 has been in urban areas and the rate in the rural areas has decreased slightly.

There is a great variation in the rate by states owing largely to variation of the Dry sentiment. The statistics show that there was no shift in age at full fledged alcoholism. This comprehensive survey is a valuable document and should be in all medical and reference libraries and in the libraries of persons interested in the subject.

*Doctor Don't Let Me Die!* By S. S. Keiner M.D. Collaborator, Dan Gordon. With an introduction by Henry E. Sigerist, M.D. 8<sup>1</sup>/<sub>2</sub> cloth, 486 pp. Boston Meador Publishing Company 1947 \$3.50.

The author writing in a fictional form has presented his views on the inadequacies of present-day medical practice and favors the passing of the Senate bill providing for a national health program. The book is essentially an autobiography.

*Pharmakologie als theoretische Grundlage einer rationellen Pharmakotherapie* By K. O. Møller ord Professor der Pharmakologie an der Universität Kopenhagen. Übersetzung und Bearbeitung nach der dritten dänischen Auflage von Dr. O. Walker 8<sup>1</sup>/<sub>2</sub> cloth 744 pp. with 34 illustrations. Basel Benno Schwabe and Company 1947 48 Swiss francs. Imported by Grune and Stratton New York N. Y.

This standard Danish work on clinical pharmacology is now available in a German language translation. The subject is treated from the viewpoints of physiology and experimental pharmacology. The author has adopted a simple classification of ten divisions as follows: organic bacterial antiseptics; substances of predominant local action; chemotherapeutics including the coal tars, sulfonamides and antibiotics; narcotics; alkaloids and other substances acting on the autonomic nervous system; cardiovascular drugs; substances predominantly acting on heat regulation and metabolism; vitamins; hormones and related body regulating substances including insulin and cortin salts, acids, bases, light metals and metalloids and heavy metals.

The material is well organized and the text well written without redundancy. Under each drug there is given the chemical formula and chemistry, pathological actions and therapeutic indications; the official preparations of the German Swiss and other pharmacopoeias are also presented. Selected references of fundamental character are appended to the drugs when considered necessary. In addition there is a forty-seven-page bibliography arranged alphabetically by authors following the text. This bibliography and the references are international in scope embracing all languages and including a good representation of American and English writers. References as late as 1945 are cited. A comprehensive subject index concludes the volume. A valuable index of definitions is printed on page 724. The publishing is excellent in every way. The type is good; the margins wide; the paper soft and the type page pleasing to the eye. Although the book is large, the weight is comparatively light for the size of the volume. It is a pleasure to handle such an excellent volume. This book should be in all medical schools, universities and large medical libraries as well as in all collections pertaining to pharmacology and pharmacy. It is hoped that an English translation will be forthcoming.



*Psychopathology A survey of modern approaches* By J Ernest Nicole, O B E, L M S S A, D P M R C P & S, medical superintendent, Winwick Mental Hospital Fourth edition 8°, cloth, 268 pp Baltimore Williams and Wilkins Company, 1946 \$4 75

In this new edition few changes have been made in the text, but the bibliography has been brought up to date so far as possible and comprises thirty-one pages made up entirely of monographs and books. The book is well printed with a good type on good paper with prewar margins. This short treatise should prove useful to persons interested in the subject.

*A Manual of the Common Contagious Diseases* By Philip Moen Stimson, M D, associate professor of clinical pediatrics, Cornell University Medical College, visiting physician, Willard Parker Hospital, director, Poliomyelitis Service, the Knickerbocker Hospital, medical director, The Floating Hospital of St. John's Guild, associate attending pediatrician, the New York Hospital, and consulting pediatrician, the Meadowbrook, Bergen Pines and Norwegian Lutheran hospitals. Fourth edition, thoroughly revised 12°, cloth, 503 pp., with 67 illustrations and 8 plates, 6 in color Philadelphia Lea and Febiger, 1947 \$4 00

A large part of this new edition of a standard, authoritative manual has been rewritten, and much new material added to the text to bring it up to date, including a new chapter on the sulfonamides and the antibiotics. The chapter on poliomyelitis is essentially new. The bibliographies appended to each disease have also been brought up to date. A number of new illustrations have been added to the book. The printing is well done with a good type on good paper with wide margins. The manual should prove useful for quick reference purposes to physicians, nurses and health officers.

*Occupational Diseases of the Skin* By Louis Schwartz, M D, medical director, United States Public Health Service, chief, Dermatoses Section and associated clinical professor of dermatology and syphilology, New York University College of Medicine, and adjunct professor of dermatology and syphilology, Georgetown University School of Medicine, Louis Tulipan, M D, clinical professor of dermatology and syphilology, New York University College of Medicine, consulting dermatologist, Manhattan General Hospital, and associate visiting dermatologist and syphilologist, Bellevue Hospital, and Samuel M. Peck, M D, dermatologist, Mt. Sinai Hospital, New York City. Second edition, thoroughly revised 8°, cloth, 964 pp., with 146 illustrations and 1 colored plate Philadelphia Lea and Febiger, 1947 \$12 50

This second edition of a standard reference book has been revised to bring it up to date. Material on new chemicals and new methods of manufacture, many developed during the war years, has been incorporated in the text. The volume is well published in every way and should be in all medical libraries, as well as in the libraries of dermatologists and physicians coming into contact with industrial dermatoses.

## NOTICES

### ANNOUNCEMENTS

Dr. Sydney J. Allman announces the opening of an office at 422 Beacon Street, Boston, for the practice of dermatology and syphilology.

Dr. William J. Clauser announces the opening of an office at 330 Dartmouth Street, Boston, for the practice of psychiatry.

Dr. A. H. Delman announces the opening of an office at 183 Babcock Street, Brookline, for the practice of otolaryngology.

Dr. Howard A. Hoffman announces the removal of his office to 60 Eighth Street, New Bedford, for practice limited to urology.

Dr. H. Sinclair Tait announces the opening of an office at 142 Main Street, Brockton, for the practice of psychiatry.

Dr. Sidney C. Wiggin announces the removal of his office to 270 Commonwealth Avenue, Boston.

## SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, October 21, at 12 noon. Dr. John H. Cauley, health commissioner, City of Boston, will speak on "Problems of the Health Department."

This meeting will mark the beginning of the twenty-first year for the South End Medical Club. Physicians are cordially invited to attend.

## MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The next meeting of the Middlesex South District Medical Society will be held at the Murphy General Hospital, Waltham, on October 22, at 12 noon, preceded by a business meeting at 11 30 a m. Various papers will be presented by members of the hospital staff. Luncheon will be served at 1 00 p m.

## NORFOLK DISTRICT MEDICAL SOCIETY

A meeting of the Norfolk District Medical Society will be held at 8 p m. on Tuesday, October 28, at the Boston Medical Library, 8 Fenway, Boston, entitled "Laher Clinic Night."

### PROGRAM

The Present Status of the Peptic-Ulcer Problem Dr. A. Allen Wilkinson

Nonsurgical Proctologic Conditions Dr. Neil W. Swinton

Chronic Urethritis in Female Patients Dr. Earl E. Ewert

All physicians are invited to attend. A collation will be served.

## CUSHING VETERANS ADMINISTRATION HOSPITAL

The following lectures will be presented at the Cushing Veterans Administration Hospital, Framingham, Massachusetts, at 4 p m. on the dates indicated.

October 24 Dr. John P. Peters, professor of medicine, Yale University School of Medicine "Some Problems of Edema"

October 30 Dr. Homer W. Smith, professor of physiology, New York University College of Medicine. "Hypertension and Urologic Disease"

October 31 Dr. Smith "Renal Circulation"

## STATE-WIDE HEALTH LEGISLATIVE CONFERENCE

The fourth Annual State-Wide Health Legislative Conference will be held in the Gardner Auditorium, State House, Boston, at 10 a m. and 2 p m., on Wednesday, October 29. All those interested in health legislation are invited to present their projects at that time and, if possible, to send word of them and any bill drawn to the Massachusetts Central Health Council, 1148 Little Building, Boston.

## AMERICAN ACADEMY OF ALLERGY

The American Academy of Allergy will hold its annual convention at the Hotel Jefferson, St. Louis, Missouri, from December 15 to 17 inclusive. All physicians interested in allergic problems are cordially invited to attend the sessions. As guests of the Academy by registering without payment of fee. The program and the scientific and technical exhibits have been arranged to cover a wide variety of conditions in which allergic factors may be important. Papers will be presented dealing with the latest methods of diagnosis and research, as well as the results of investigation and research. Round-table conferences will be held on Monday afternoon, December 15. Advance copies of the program may be obtained by application to Dr. Charles H. Eyerly, chairman on arrangements, 634 North Grand Boulevard, St. Louis, Missouri.

(Notices continued on page xvii)

# The New England Journal of Medicine

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Volume 237

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Number 17

## CRITIQUE ON VAGOTOMY

WILLIAM R. MOSES, M.D.\*

WASHINGTON, D. C.

AT LEAST fifty surgical procedures have been employed in the cure of chronic peptic ulcer since Doyen<sup>1</sup> first suggested gastroenterostomy, nearly all of which have been based on arrest or neutralization of acid secretion. The operation of the hour is vagotomy, which owes its popularity to the imperfections of its immediate predecessor, subtotal gastrectomy.

The criticisms of the end results of gastrectomy have been directed toward postoperative marginal and secondary ulcers, postoperative nutritional impairment, dyspepsia, diarrhea, defective fat absorption, secondary anemia, incomplete relief of pain, subsequent hemorrhages and "vagotonic symptoms." Postoperative ulceration is reported in 2 to 6 per cent of cases by Moore,<sup>2</sup> Zollinger,<sup>3</sup> and Hollander and Mage,<sup>4</sup> 3.1 per cent of 225 cases by Berg,<sup>5</sup> 6.9 per cent of 173 cases by Kiefer<sup>6</sup> and in over 100 cases collected by Hurst.<sup>7</sup> Loss of weight has been noted in 10 per cent of 230 cases by Miller,<sup>8</sup> 30 per cent by Ingelfinger,<sup>9</sup> 47 per cent by Church and Hinton<sup>10</sup> and 66 per cent by Browne and McHardy.<sup>11</sup> Ingelfinger<sup>9</sup> found persistent postcibal symptoms, such as postprandial hypoglycemia, in 10 per cent. Diarrhea of minor degree is seldom encountered. Impairment of fat, but not of carbohydrate or protein, is rarely seen, but secondary anemia is frequent. Recurrence or incomplete relief of pain occurred in 36 per cent of cases according to Church and Hinton<sup>10</sup> and in 40 of 502 cases in Colp's<sup>12</sup> series. Subsequent hemorrhages followed 4.6 per cent of resections in Kiefer's<sup>6</sup> report, and mild "vagotonic" symptoms in 10.2 per cent of Berg's<sup>5</sup> 225 patients. Miscellaneous "failures" are claimed in 10 per cent of Gatewood's,<sup>13</sup> 30 cases and in 8 per cent of 26 cases studied by Garrett.<sup>14</sup> Rienhoff<sup>15</sup> believes that a certain number of complications are inevitable when gastric and jejunal mucosae are joined. In justice to the operation, however, it should be emphasized that its candidates are culled mainly from those refractory to medical management, that these reports do not represent general surgical experience and that the results of

the procedure in gastric as opposed to duodenal ulcer are consistently gratifying. Less than 1 per cent of these patients have further trouble.<sup>17</sup> According to Walters<sup>18</sup> marginal ulcer is almost unknown after resection for gastric ulcer. Finally, an operation for chronic duodenal ulcer that results in an average of 15 per cent failures in medically intractable cases is hardly ready for discard.

Although comparative results of medical and surgical therapy can be treacherous, a recent survey by Krarup<sup>19</sup> is of interest. This study, based on the results of medical treatment after five years in 665 patients, reveals that only 29 per cent had a complete recovery, 36 per cent were improved and 35 per cent had a poor result. In the patients with gastric ulceration the relapse rate was 86 per cent, and those with chronic duodenal ulcer showed only 20 per cent complete recovery.

No surgical attack on chronic peptic ulcer can do more than break a link in the chain of ulcer pathogenesis, since the basic cause remains unknown. The factors modified, or supposedly modified, by vagotomy may be grouped as gastric secretion, gastric motility and gastric visceral sensation.

### GASTRIC SECRETION

The hypothesis implicating hydrochloric acid excess in the pathogenesis of ulcer has recently been challenged by Sandweiss,<sup>20</sup> who found normal quality and quantity of secretion in patients with chronic ulcer but who agreed that this acid is irritative to the existing ulcer, he suggests that the stomach of the ulcer patient retains the acid for an abnormally long time—a view that is in conflict with the more generally accepted one of hypermotility. According to Palmer,<sup>21</sup> there is abundant evidence that gastric secretion in patients with ulcer is above normal in acidity and quantity. Peptic ulcer, however, cannot be produced experimentally by perfusion of the intestine with any physiologic concentration of hydrochloric acid.<sup>22-24</sup> Despite the dictum of Schwarz<sup>25</sup>—"no acid, no ulcer"—achlorhydria was noted by Vanzant<sup>26</sup> with about half its frequency in the general population. Vanzant found that whereas the average duodenal

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ulcer has an acidity of 12 units above normal, the average gastric ulcer is accompanied by an acidity of 6 units below normal. Bloomfield<sup>27</sup> supported the general view that basal acid levels are increased in ulcer but observed normal levels on histamine stimulation. Acid values and total secretion are stated as increased in both types of ulcer by Sagal,<sup>28</sup> in duodenal ulcer alone by Bloomfield,<sup>29</sup> in the cephalic phase alone\* by Necheles and Maskin<sup>32</sup> and in all three digestive phases in duodenal but not in gastric ulcer by Ihre.<sup>33</sup> Dragstedt and his associates<sup>34-43</sup> and Best<sup>44</sup> consider vagal hypertonus with hyperacidity, hypersecretion and hypermotility as pathogenetic. Hurst<sup>45</sup> recorded increased acidity and total secretion in 60 per cent of cases but questioned whether the finding is the cause or the effect of the lesion.

The role of pepsin, rather than acid, has been emphasized by Schiffrin and Ivy,<sup>22</sup> Ihre,<sup>33</sup> Schiffrin and Warren,<sup>46</sup> Büchner,<sup>47</sup> Varco,<sup>48</sup> Bucher and Ivy,<sup>49</sup> Shoch and Fogelson<sup>50, 51</sup> and Schiffrin and Warren.<sup>52, 53</sup> The data include the discoveries that experimental ulcer cannot be produced by acid alone but can be caused if pepsin is added,<sup>22, 46, 52, 53</sup> the finding of increased pepsin in the stomach of the animal with experimental ulcer<sup>47-49</sup> and in man with ulcer<sup>33</sup> and the preservation of health in dogs with histamine-produced ulcer by simultaneous administration of sodium lauryl sulfate, which neutralizes pepsin without affecting acid.<sup>50, 51</sup>

Dragstedt has repeatedly emphasized the role of continuous secretion in the persistence and initiation of chronic ulceration. This continuous secretion, which is estimated as from 10 to 117 cc an hour by Carlson,<sup>54</sup> Ivy<sup>55</sup> and Ihre,<sup>33</sup> may be abolished by atropinization, but the atropine effect is lost if an ulcer is present.<sup>56</sup> The biochemical effects of vagotomy are listed by Moore<sup>2</sup> as a drop of free hydrochloric acid to zero during most of the day, a rise of the reaction by 1 to 3 units constantly, a reduction of total acid, a mild drop in chlorides, no essential change in pepsin or total base and considerable reduction of total secretory volume.

In animals Pavlov<sup>57</sup> was the first to demonstrate gastric secretory fibers in the vagi and noted a loss of response to sham feeding after their section. Hartzell<sup>58</sup> produced a marked drop in free and total acid by vagotomy, but Vanzant,<sup>59, 60</sup> studying the same dogs, found a gradual return to normal values in two or three years. Although Hartzell's work was confirmed by Dragstedt,<sup>36, 38</sup> others have failed to do so in dogs<sup>61-63</sup> and monkeys.<sup>64</sup> Peptic ulcer has been caused in dogs by prolonged vagal stimulation.<sup>65</sup> Mann-Williamson dogs, which normally develop marginal ulceration, can be protected by vagotomy.<sup>66</sup> Ingestion of food results in a rise in gastric acid even though vagotomy has been

performed.<sup>67</sup> Vagal stimulation causes an increase in both acid and pepsin.<sup>68</sup>

### GASTRIC MOTILITY

According to Best and Taylor<sup>68</sup> vagal stimulation may cause either inhibition or stimulation of the gastric musculature, the effect being opposite to the pre-existing tone, but Wiggers<sup>69</sup> believes that the chief vagal effect is to increase the contractions while relaxing the pylorus. Dragstedt, Best,<sup>44</sup> MacKay<sup>41</sup> and Shay<sup>70</sup> have found hypermotility as characteristic of the ulcer case, but Quigley<sup>71</sup> states that most investigators have recorded normal motility, whereas Rivers,<sup>72</sup> Todd<sup>73</sup> and the group of Sandweiss note decreased motility.

No such confusion regarding gastric motility is encountered after vagotomy, all authors reporting consistent, considerable and, at times, troublesome gastric atony with almost complete absence of hunger contractions, initial gastric emptying increased to fifteen or twenty minutes as compared to the normal of a half to one and a half minutes and complete emptying requiring fifteen to twenty-four hours in contrast with the normal of two to two and a half hours, this atony being typically limited to a few weeks or months.

### GASTRIC VISCERAL SENSATIONS

The tenets of Hurst<sup>7</sup> are accepted by most observers, who believe that the pain of peptic ulcer is due to spasm of the gastric musculature. Quigley<sup>71</sup> holds that the pain is caused by violent hunger contractions, which are stimulated by mechanical irritation of the ulcer by food, fasting, elevated metabolic rate, cold, diabetes or hypoglycemia and inhibited by bland foods, smoking, pain and emotions. Direct chemical irritation of the nerve endings in the ulcer are considered the cause of the pain by Dragstedt and Palmer,<sup>21, 42</sup> who reproduced pain without associated pylorospasm in human beings by direct acid application to the ulcer.

Whatever the mechanism of pain, its relief after vagotomy is dramatic and so consistent that post-operative absence of the phenomenon should suggest either inadequate operation or inaccurate diagnosis. Since radiologic and gastroscopic evidence of healing is delayed for one to three weeks and the relief is seen even when gastric secretion is relatively unaltered, one must suspect that the relief is neurogenic, even though it has been shown that afferent sensation from the stomach — as noted by response to hot and cold liquids, balloon distention and gastroscope traction — is unaltered. Dragstedt stated that the ingestion of acid after vagotomy reproduces ulcer pain, a contention not confirmed by Smith,<sup>74</sup> who concluded that pain is abolished by loss of ability of the stomach to enter the spastic state as a result of paralysis of its extrinsic nerve supply.

\*The phases of gastric secretory response are classified by Schiffrin and Ivy<sup>22</sup> and Ivy, McIlvaine and Javols<sup>50, 51</sup> as follows: cephalic phase, response to appetite, dependent on vagal tonus; abolished by atropine; gastric phase, stimulated by mechanical distention and secretion, not under vagal control; and intestinal phase, provoked by food, intestinal secretagogues.

### CRITICISMS OF VAGOTOMY IN THE DEFINITIVE TREATMENT OF ULCER

Although Dragstedt was the first to obtain successful results with vagotomy, the procedure was first employed by Latarjet<sup>16</sup> in 1922, with early relief but later recurrence of distress. In 1930 Pien and Tanferna<sup>16</sup> reported its use both above and below the diaphragm in 8 cases, with early depression but later restitution of acid after two years.<sup>17</sup> In 1944 Weinstein<sup>18</sup> found that resection of the vagi above and below the diaphragm in 6 cases had neither reduced acid nor afforded clinical benefit, a belief supported by animal experiments. Vagotomy has been criticized on the ground that it delays the passage of food into the duodenum and thus interferes with secretion of the hormone enterogastrone, which is normally released on contact of the duodenal mucosa with fat,<sup>22</sup> "inhibits gastric secretion and motility"<sup>23</sup> and is believed to be of value in preventing experimental jejunal ulcer,<sup>24</sup> an effect also claimed for urogastrone.<sup>25</sup> A further criticism is that the delayed gastric emptying results in prolonged contact of acid with gastric mucosa, and that the vascular supply to the stomach is decreased.<sup>26</sup> An unfavorable view of the operation is taken by Sandweiss,<sup>27</sup> who objects to the numerous disturbances of intestinal function, the partial denervation of the pancreas and duodenum and the loss of "receptive relaxation" of the duodenum. Most observers have failed to demonstrate any important effects on pancreatic function.<sup>28</sup> Ivy<sup>29</sup> fears the predisposition to gastric atony and achalasia. Others will be disturbed by the failure to reduce pepsin secretion. Although a review of the literature shows that free acid is abolished in only half the cases and has a tendency to rise again after several months, proponents of the procedure believe that benefit has nonetheless resulted because the stomach is robbed of its ability to secrete super-concentrated acid juice during anxiety periods.

The technical difficulty of severing all vagal supply to the stomach by any approach has been emphasized,<sup>30</sup> "and most modern enthusiasts have explained the consistent failures of the pioneer vagotomies by lack of thoroughness of the operation and failure to prevent regeneration of the fibers. White and Smithwick<sup>31</sup> have emphasized this remarkable ability of autonomic nerves to regenerate, a propensity that Moore has attempted to check by interposing the diaphragm between the cut vagi and Dragstedt has combated by using the parietal pleura as a block.

Although vagotomy per se is not criticized, its use should be avoided in the management of gastric ulcer. The resection for gastric ulcer is an exceptionally satisfactory operation, is attended by a mortality in capable hands of about 2 per cent, has consistently satisfactory end results and is almost never followed by recurrence or marginal ulceration.

Secondly, earlier resection of borderline lesions provides the single hope of improving the present egregious cure rate in patients with gastric cancer, less than 5 per cent of whom now survive five years. Using presently available diagnostic criteria, only the pathologist is able to differentiate gastric ulcer from early carcinoma. The radiologist, on whom this grave responsibility is usually thrust, fails in this differentiation in from 10 to 24 per cent of opportunities.<sup>17</sup> "18" "19" When it is considered that cases so misdiagnosed represent the only group in which effective strides in the reduction of mortality from gastric cancer can be expected, these figures command respect out of proportion to their arithmetic values.

In my opinion, the most serious criticism that may be directed at vagotomy is that there is no incontrovertible evidence that it corrects the faults in the pathogenesis of ulcer, for the excellent reason that, despite the considerable physiologic alterations and consistent relief of pain, there is no proof that the factors so altered were at fault before the operation. The explanation of pain relief proposed by Smith<sup>32</sup> has been convincingly presented. Concerning ulcer healing, one must consider the consistent psychosomatic pattern peculiar to ulcer victims and the effects of medical and surgical suggestion in the neurotic type. All previous curative operations for ulcer were attended by phenomenal "cure" rates in their zeniths. Perhaps the ulcer-pain-ulcer syndrome is a vicious circle, which may be interrupted merely by relief of pain, but this hypothesis must await proof. In 2 cases reported recently by Weeks et al.<sup>33</sup> fatal perforations of the ulcer followed vagotomy despite the relief of pain.

### COMPLICATIONS OF VAGOTOMY

In this discussion the complications that are specific to the incisions, thoracotomy and laparotomy, or to anesthesia are omitted. The elimination of these, however, leaves certain actual or theoretical complications that are peculiar to vagus resection, such as failure to reduce gastric acid or its later recurrence, failure to effect ulcer healing or its recurrence, symptoms of gastric dilatation or pyloric obstruction, severe and persistent pain in the operative site, postoperative diarrhea, reduction of vascular supply to the stomach, cardiac and respiratory reflex effects and achalasia of the cardiac sphincter.

Although free gastric acid is completely abolished in about 50 per cent of cases, many have noted the inconsistent and unpredictable results in this respect.<sup>30</sup> "31" "32" and these observations support the belief that reduction of acid is not the essential factor in relief of symptoms. Dragstedt<sup>34</sup> failed to abolish the cephalic phase of digestion as shown by response to a sham meal in 30 per cent of one series. In the Duke series even patients with an immediate achylodynia demonstrated a return of acid within

several months<sup>74</sup> — a result anticipated from experience in animals<sup>60</sup> There is no apparent effect on the gastric phase of acid secretion as shown by normal response to caffeine and histamine, which act directly on the gastric cells

The insulin test\* of vagal intactness, popularized by Dragstedt, is in general use as a test of adequacy of vagal section, and it is said that ulcer recurrence is unknown in cases in which the test has remained negative The Duke group, however, found that the results of the test are inconclusive<sup>74</sup>

Ulcer healing after operation is not invariable, nor does healing guarantee against recurrence, as is shown by 1 case of early recurrence in the Duke series of 50 cases,<sup>74</sup> 2 noted by Crohn,<sup>85</sup> 1 by Dragstedt<sup>38</sup> in an early report and 6 patients with continuing distress in a later review<sup>36</sup> Two fatal perforations after vagotomy have been recorded above Weinstein<sup>61</sup> noted no benefit in 6 patients studied One recurrence and a postoperative stomal ulcer were encountered by Moore<sup>2</sup> Curious and interesting has been the spontaneous development of gastric ulceration in vagotomized dogs and rabbits living under hardship conditions<sup>103, 104</sup>

Postoperative gastric retention occurs in almost all patients, although not usually to a degree sufficient to cause undesirable symptoms Vomiting of transient or persistent nature, however, is the most frequent serious complication Although marked gastric atony is usually limited to a few days, relative lack of motility lasts for several months, and if combined with narrowing of the pylorus or duodenal cap, due either to cicatrix or to edema, intractable vomiting will result Such sequelae were noted by Dragstedt<sup>36</sup> in 3 cases, by Moore<sup>2</sup> in 1 case and in 10 per cent of the Duke series,<sup>74</sup> most of these patients requiring a second operation for relief of the obstructive phenomena Occasional fullness and regurgitation were noted in half of 31 cases studied by Smith,<sup>74</sup> who found that mecholyl, prostigmine and doryl were of no value, but urecholine, suggested by Machella, was helpful in 4 cases in which it was used If there is evidence of pyloric obstruction, either seen by the radiologist or felt by the surgeon, vagotomy should not be performed unless combined with gastroenterostomy, gastric resection or pyloroplasty

Moderate to severe pain along the course of the intercostal nerves when the procedure is performed through the chest is frequent and often prolonged for six to twelve weeks Section of the nerves during operation does not modify the discomfort, which is due either to crushing of the nerves between ribs jammed together by the rib spreader or to subluxation of the ribs at their sternal or vertebral attachments Abbott<sup>105</sup> has used bromsalizol intercostal-

nerve block to relieve this pain during the first four to ten days after operation

In the Duke series diarrhea was recorded in 54 per cent, being of extended duration in 16 per cent<sup>74</sup> It was not relieved by the administration of acid by mouth, nor were there any abnormalities of stool fat The symptom has been recently explained on the basis of jejunitis

The criticism that vagotomy reduces the vascular supply of the stomach<sup>22</sup> seems of dubious importance in view of the normally excessive blood supply although Smith<sup>74</sup> reports a fatal case of rupture of pyloroplasty suture line among 6 cases in which vagotomy was combined with other gastric operations Since pyloroplasty is often performed in scarred areas of decreased vascularity and in patients with general malnutrition, the role played by vagotomy in this accident is impossible to evaluate

Cardiac arrest under anesthesia during manipulation of the vagi has been reported in at least 2 cases,<sup>2, 90</sup> apparently owing to a "vagovagal" reflex — an effect that Moore<sup>2</sup> has avoided by the use of large doses of atropine before and during operation, in addition to novocainization of the nerves before manipulation The high incidence of pneumonia (22 per cent) in the Duke series suggests that vagal manipulation predisposes to respiratory complications — a suspicion that is supported by experimental evidence in animal and man that vagal stimulation may produce slowing or arrest of the heart, fall of blood pressure, possible contraction of the coronary vessels and constriction of the bronchial system<sup>67 106-119</sup>

Although Ivy<sup>84</sup> stated that vagotomy predisposes to achalasia of the cardiac sphincter, the literature has been free of reference to this complication It is difficult to understand why cardiospasm is not the usual effect White and Smithwick<sup>86</sup> observe that the innervation of the esophagus includes the parasympathetic nerves, whose stimulation increases peristalsis of the esophagus and opens the sphincter, and the sympathetic, whose function is to inhibit peristalsis and close the sphincter The vagi supply the organ directly as they lie in close contact with it in the lower third The sympathetic motor and viscerosensory fibers arise from the fifth and sixth thoracic ganglions and those of the aortic arch The lower esophagus and cardiac sphincter get their supply by way of the descending aortic plexus and splanchnic rami, running through the celiac ganglions and passing along the branches of the celiac artery, mainly the left gastric artery Animal investigation of the effect of the vagus on the sphincter is confusing, some finding that the nerve is primarily a dilator to the muscle<sup>120-122</sup> and others that it is a constrictor<sup>123-126</sup> Most physiologists<sup>127-132</sup> believe that the dilatation of the esophagus after vagectomy is compensatory to spasm of the sphincter Vagotomy in animals has been shown to result consist-

\*This test developed from the studies of many observers<sup>84-102</sup> who found that insulin hypoglycemia increases gastric motility and secretion — an effect that is dependent on the intactness of the gastric fibers of the vagus In the test sufficient insulin, usually 20 to 30 units, is administered to lower the blood sugar below 50 mg per 100 cc. and is followed by intermittent gastric aspirations

ently in achalasia<sup>123 125-126</sup> — an effect that may be prevented by previous or simultaneous sympathetomy<sup>122-123</sup> Knight and his associates<sup>122-123</sup> and others<sup>125-126</sup> have applied this experimental evidence clinically by sympathetic denervations of the gastric cardia in spontaneous achalasia, generally with indifferent results<sup>122 124</sup> Knight has explained the poor results obtained in other hands on the basis of failure to select amenable cases. He classifies muscular obstructions of the lower esophagus as achalasia of the cardia (due to vagal failure), cardiospasm (due to spasmodic contraction, a reflex disorder of other diseases, such as ulcer, esophagitis and neurosis) and hypertrophic stenosis of the cardia (exactly analogous to hypertrophic stenosis of infants). The first two conditions show no true obstruction and no muscular hypertrophy at autopsy, and both respond to sympathetomy. In the third type, the obstruction persists even after death and is, of course, unresponsive to sympathetomy. It seems that novocain block of the sympathetic nerves, followed by esophagram or esophagoscopy, should differentiate the types and suggest proper management. In the United States the favored operation is esophagostomy.

The following is believed to be the first case report in which achalasia has been encountered after vagotomy.

J. H. S., a 44-year-old man, was admitted to Providence Hospital on October 28, 1946 with a history of 6 months duration during which he had suffered almost constant pain in the epigastrium and left upper quadrant partially relieved by the ingestion of sodium bicarbonate but not completely relieved by any measures including opiates. This interval was associated with a loss of 15 pounds in weight and intermittent red and tarry stools. In February 1945 a gastric resection had been performed for chronic duodenal ulcer after which the patient had been well until April 1946. Barium studies prior to admission revealed a marginal ulcer. Laboratory studies of the blood demonstrated only a secondary anemia. Gastric analysis recorded the free fasting hydrochloric acid as 62 units rising to 94 units after histamine administration.

On October 31 supradiaphragmatic vagotomy was performed followed by Wengenstein suction for 72 hours with progression to a soft diet on the 5th postoperative day.

On November 7 the patient remarked that his food seemed difficult to swallow but was reassured that the symptom was probably due to edema of the esophagus caused by manipulation, and was discharged on the following day, being greatly impressed with the total absence of abdominal pain since the first postoperative day.

On November 10 I was called to his home by the patient's wife, who stated that he was 'choking to death' after eating some bread. He was attempting to vomit without effect and complained that the bread was stuck under the lower sternum, a sensation that was suddenly relieved after a swallow of water. An esophagram within 1 hour revealed the upper three-fourths of the organ to be slightly dilated whereas the lower 5 or 6 cm. was invisible for 4 minutes during which the barium column showed no change in level other than fluctuations coinciding with respiration. Gradually the barium began to trickle through the cardiac sphincter into the stomach. Three days later during which the patient was unable to swallow anything but small, frequent liquid feedings the esophagram was repeated with the same findings. A celiac ganglion block was then performed under bromsalizol after which the esophagram revealed normal transit. For the following 5 days the patient was able to swallow solid food without difficulty but on November 19

the symptoms recurred. Bromsalizol block was repeated on November 20 with the same results. On November 29, after a recurrence of symptoms, the block was again attempted but the aorta was entered and the procedure was abandoned. Symptoms persisted for another week in milder degree than previously and then gradually disappeared. On December 14 the final esophagram revealed normal transit of barium although the esophageal lumen was dilated to twice its normal size. The marginal ulcer has healed radiologically and clinically and a weight gain of 17 pounds has since been noted.

This case demonstrates achalasia of the cardiac sphincter following vagotomy with symptoms of obstruction persisting for five weeks after operation. This is believed to be the first case report of this complication after section of the vagi, and is apparently the first of its treatment with celiac-ganglion blocks. It is impossible to know whether the final relief was due to bromsalizol, although the temporary alleviation may justifiably be assigned to the drug. That achalasia following vagotomy in animals has a tendency to spontaneous resolution has been suggested by Cannon,<sup>122</sup> although Knight<sup>123</sup> believes that spasm persists but is functionally overcome by compensatory strengthening of the proximal esophageal peristalsis.

#### SUMMARY

Vagotomy in the therapy of peptic ulcer owes its popularity to the immediate and delayed imperfections of gastric resection. These criticisms of gastrectomy comprise postoperative recurrent and marginal ulcers, nutritional impairment, dyspepsia, diarrhea, defective fat absorption, secondary anemia, incomplete relief of pain, subsequent hemorrhages and "vagotonic symptoms," whose incidence collectively is about 15 per cent. The most serious delayed complication is marginal ulcer, which follows approximately 5 per cent of resections for duodenal ulcer. In competent hands the procedure will carry a mortality of about 3 per cent when the lesion is duodenal.

Medical therapy for peptic ulcer is not so successful as is generally believed, relapses being frequent and actual permanent relief occurring in as few as 30 per cent.

Gastric, as opposed to duodenal, ulcer should never be treated by any means other than gastrectomy, especially in the age group above thirty-five years. The inability of any available diagnostic measures to differentiate early carcinoma from benign ulceration with reliable consistency is well established. Secondly, gastric resection for gastric ulcer is an entirely satisfactory operation, almost never being followed by marginal ulceration. The mortality should not exceed 1 or 2 per cent, being lower than that in duodenal ulcer because the biliary structures are not in peril and the suture rows are placed in healthy duodenal tissue, minimizing the risk of blow-out of the duodenal stump.

Although semipermanent cures of ulcer are fairly consistently observed after vagotomy, the mecha-

nism of such cure is unknown, and its permanency cannot be measured within a generation. Not only is the pathogenesis of ulcer unknown but also there is lack of clinical and experimental proof supporting alleged disturbances of secretion and motility.

The salient effects of vagotomy on the stomach are a marked decrease in quantity and acidity of gastric secretion, although there is a strong tendency toward subsequent restoration to normal values, and impressive inhibition of gastric motility, also tending toward restitution. This depression of contractility of the stomach is of such a degree that vagotomy must not be used alone if there is evidence of pyloric or duodenal narrowing, but must be combined under such circumstances with gastroenterostomy or pyloroplasty.

The reported complications of vagotomy have been increasing in number and variety. The ulcer crater has occasionally failed to heal, or having healed, has recurred in a few cases. Whether this represents inadequate operation is unknown, but it must be emphasized that a most careful search should be made to assure interruption of all fibers. Gastric dilatation should be prevented by adequate postoperative suction and by cautious intake of food when some return of gastric tonus obtains. Persistent symptomatic gastric retention denotes some degree of pre-existing pyloric obstruction and contraindicates the use of vagotomy alone. Persistent pain in the operative area may be decreased by less vigorous rib spreading, by resection of two ribs to allow better exposure with less retraction or by the use of the abdominal approach. Cardiac asystole during operation may be avoided by adequate atropinization. What is apparently the first case of achalasia after vagotomy in man is reported, and its management with bromsalizol celiac-ganglion blocks is discussed.

Vagotomy is indicated in two situations as the procedure of choice—marginal ulcer, whose relief by conventional means involves a procedure of first magnitude in a patient usually in only fair or poor condition, and duodenal ulcer, especially the type penetrating the pancreas or involving the area of the common bile duct or ampulla. These are the types that contribute most to mortality rates and technical difficulties.

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## COCCIDIOIDOMYCOSIS IN NEW ENGLAND

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**C**OCCIDIOIDOMYCOSIS, probably the most infectious of the systemic mycoses, is rarely found along the Atlantic Seaboard. Owing to the tremendous displacement of people from their native areas that occurred during the war, however, clinicians must be aware that these infections may occur among the population, particularly in persons who have seen service in endemic coccidioidomycotic areas. A carefully taken history in patients who present granulomatous conditions of the skin and bizarre pulmonary lesions, either of cavitation without surrounding exudation or of ring-like apical formations with negative-tuberculins, as well as a period of residence in areas where coccidioidomycosis is present, should make one suspicious of this condition.

The purpose of this article is to report a series of 4 cases of coccidioidomycosis found in servicemen who had returned to their native environments, particularly in the area of New Hampshire and Vermont, with lesions that resulted in the determination that they had sustained coccidioidomycotic infections. One of these cases presented a severe granulomatous condition of the skin that was not recognized for a long time, was extremely disfiguring and responded to therapy only after many extensive trials with penicillin, streptomycin, sulfonamides, iodides and x-ray therapy alone and in combination with penicillin.

The pathologic process may be divided into two clinical phases—namely, the primary type of coccidioidomycosis, particularly of the pulmonary variety often spoken of as "valley fever" or "San

Joaquin fever," which has its early infection some nine days after exposure and is characterized by mild upper respiratory manifestations such as a low-grade fever—(temperatures of 99 to 101°F) and the type having backache and headache. In some of these primary cases, skin lesions resembling erythema nodosum occur and then disappear after a few days. All primary infection and roentgenographic evidences of pulmonary disease are frequently lacking, and when infiltrations of the lung occur, they are usually small and resolve within several weeks. In some cases the lesions show progression rather than spontaneous resolution, and with rare exceptions, no primary cutaneous infections are reported. In the majority of cases, however, the disease progresses into the phase of remission, and the asymptomatic patient usually continues for a long period until—by either a routine x-ray film or, as in 1 case reported below, a cutaneous lesion manifests itself—the process is recognized. In cases that go on to terminal courses, the symptoms are often referable to organs showing a mass of lesions, especially the lungs, the lymph nodes, the meninges and, occasionally, the skin. Clinically, roentgenographically and anatomically these visceral lesions may resemble tuberculosis, blastomycosis or one of the lymphomas.

From an x-ray standpoint, the lesions in the films usually demonstrate one of several patterns. In the early stages they may show nothing but soft, fuzzy, hilar thickenings, if the disease is more advanced, examination may disclose a pneumonic type of infiltration usually extending from the hilus into the middle or lower lung fields. In cases that have undergone recrudescence, to which this paper is largely confined, the most characteristic finding is

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that of well isolated and well circumscribed, nodular lesions in the parenchyma of the lung. Such nodules are 2 or 3 cm. in diameter, occurring most frequently in the middle or lower lung fields. They usually occur singly, but sometimes they are multiple. The lesions are benign in character and after a period of months they either resolve or develop into thin-wall, cyst-like cavities. Such cavities may disappear and shrink to small nodules, which may become calcified, or they may persist for years. In 1 case, in frequent follow-up examinations, the cavity regressed and increased in size on several occasions, although the patient was asymptomatic.

The diagnosis is usually sustained by a positive skin test using the antigen of *Coccidioides immitis* or, in the patients with skin lesions, by a biopsy from the granulomatous area. The organism is easily recognized as a large (20 to 80 microns in diameter) cell whose wall is thick and doubly refractile and occasionally shows a fringe of radiating eosinophilic substance projecting from its outer layer. In all the cases presented below we were able to obtain positive skin tests to the coccidioidomycotic antigen supplied by Dr. C. E. Smith, of the University of California, and in the case with skin lesions we were able to substantiate the diagnosis by the biopsy method (Fig. 1).

The first case was observed by virtue of the fact that the patient presented himself for treatment be-

treated unsuccessfully on the outside for six months to a year without any improvement, and the under-



FIGURE 1. Photomicrograph of a Biopsy Specimen from the Skin. This shows a typical coccidioid organism.

lying picture was not ascertained until his arrival for definitive hospitalization.

#### CASE REPORTS

CASE 1. E. R., a 34-year-old machine worker residing in Manchester, New Hampshire, entered the hospital on Sep-

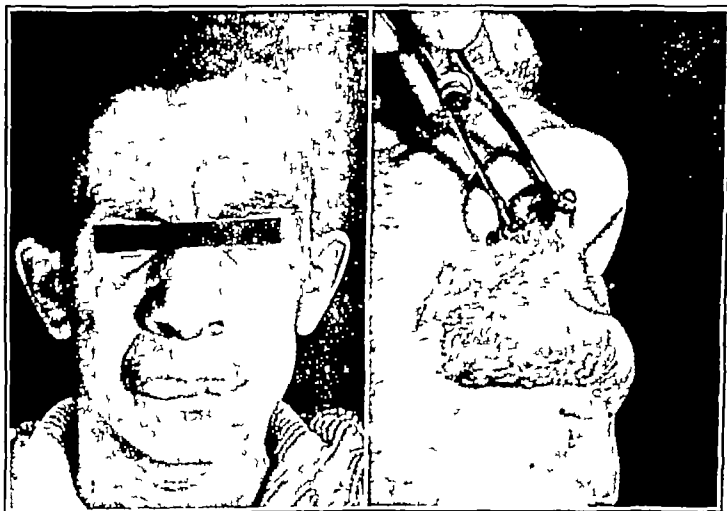


FIGURE 2. Photographs Showing the Swelling of the Upper Lip and the Nasal Lesion on the Right.

cause of the development of a severe, ulcerative, granulomatous lesion of the nose, which had been

tember 9, 1946, with a history of a swelling of the upper lip of 10 weeks' duration. He stated that for the previous year he had had an ulceration on the inner medial portion of the

left nostril that had resisted all methods of treatment and, for 6 months prior to admission, had also occurred in the right nostril. Ten weeks before admission a severe, pronounced swelling of the entire upper lip, with excoriations on the mucosal side of the lip and with cracking and fissure formation, had developed. The patient stated that about 1 year previously, in the Normandy invasion of 1945, he had been awakened suddenly while sleeping under a wagon and, in his haste to arise, had struck his left cheek against the

two deep fissures measuring 1.5 cm in length dividing the upper portion of the lip. In addition, the nose revealed a crusted ulceration on the border of the inner side of each nostril (Fig 2), the ulceration was grayish and measured 1.5 cm in diameter. The entire encrusted area was granular in appearance and dry, and there was no exudate. The lesion felt hard to the touch. Examination of the rest of the system was essentially negative. The chest expansion was good, no rales were heard either at the apices or at the bases, and

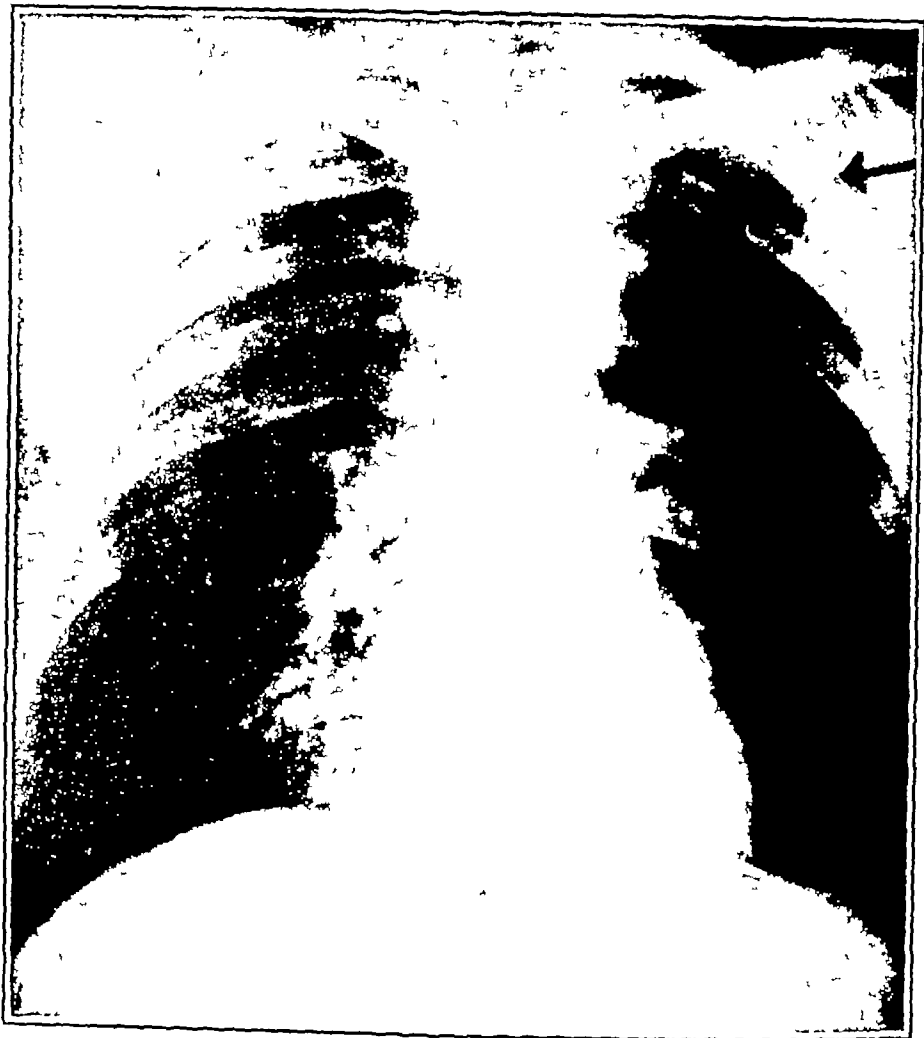


FIGURE 3 Case 1

*This roentgenogram of the chest, taken shortly after admission to the hospital, shows a ring-like shadow of increased density in the first interspace*

tongue of the wagon. This incident had been followed by swelling of the left cheek for a period of 2 weeks. When the swelling of the cheek had subsided the small, ulcerative area in the left nostril, which persisted to the date of his discharge from the Army and to the time of admission, had developed. In the statement of service it was revealed that this patient had been a corporal in the Field Artillery and had served from June, 1943, to December, 1943, in the Indio Desert, California. At the time of his service there he had never been ill, he remembered having nothing other than a mild respiratory infection for which he did not think he had required treatment.

The past history was essentially noncontributory, except for chicken pox in childhood and a hemorrhoidectomy in 1941. The venereal history was entirely negative.

Physical examination revealed a large swelling of the entire upper portion of the upper lip (Fig 2), with encrustation of the mucous membrane of the inner side of the lip and

there was no change in the character of the breath sounds. No other skin lesions were noted.

The blood pressure was 105/80.

Examination of the blood disclosed a red-cell count of 5,260,000, with 16 gm of hemoglobin, and a white-cell count of 6950, with 67 per cent neutrophils, 26 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils and 2 per cent basophils. Urinalysis was normal, and the Mazzini and Frei tests were negative. A test smear for Vincent's organism of the lesion was also negative, as was a skin test for tuberculosis and a patch test. The sedimentation rate was 4 mm in 1 hour. X-ray examination of the chest showed scoliosis of the dorsal spine and convexity to the left at the fifth dorsal segment. The trachea was in the midline. Both leaves of the diaphragm were clearly outlined, and the costophrenic angles were clear. The right lung field was essentially clear, and the left revealed a ring-like shadow of increased density in the first interspace, with a slight increase

in the bronchial markings radiating toward it (Fig. 3). X ray findings were interpreted to suggest an old acid fast infection that had been controlled.

A biopsy of the encrusted area of the lips and of the ulcerated areas of the nose was performed 2 weeks after admission. The pathological report showing tubercles containing giant cells filled with fungi. The fungi revealed a high refractile border without budding and with endosporeulation. This was consistent with the picture of cutaneous coccidioidomycosis.

A review of the x ray films of the lung at that time showed a picture more consistent with coccidioidomycosis than with

the patient made a remarkable response. The swelling decreased rapidly to the point that it was only slightly noticed.

Two months later a second biopsy was performed by the taking of a section from the skin area of the inner side of the nostril, with the following report: A firm gray white fragment measuring 0.3 cm. reveals squamous epithelium overlying inflamed connective tissue. There is no evidence of specific inflammation.

A second course of radiation given at the Mary Hitchcock Clinic by Dr. Leslie Sycamore consisted of 400 r to the lip and 400 r to each side of the face to a total of 800 tumor



FIGURE 4 Case 3

*In this roentgenogram there is a circumscribed cavitation in the right upper lobe*

tuberculosis. A skin test for *C. immitis* was positive. The patient was given 1 gm. of sulfadiazine every 4 hours, with equal amounts of sodium bicarbonate, for 7 days without any change in the character of the lesion. This was followed by 0.6 gm. of potassium iodide daily with similar poor results. The patient was then placed on 1 gm. streptomycin daily being given 0.25 gm. every 6 hours so that he received in all 30 gm., without any result. Penicillin, in doses of 50,000 units every 4 hours for 10 days, was then administered without any improvement. This was followed after a rest period of 8 days, by five doses of x ray therapy of 200 r each on alternate days to the lip and the ulcerative area so that he received a total of 1000 r. Approximately 10 days later the entire lip became macerated and red and the edema increased until the lip was twice the normal size. Because of the intensity of the reaction penicillin in massive doses was given the amount being 10,000,000 units in 7 days to which

dose r. This resulted in complete recession of the lip and nostril lesions, with loss of the edema.

During all this treatment there was no change in the character of the lung lesion.

CASE 2. A. P. a 22-year-old man whose home was in Manchester New Hampshire gave a history of having been admitted to a hospital at Laredo, Texas on November 18, 1943 for headache, dizzy spells, heartburn and palpitation of several years duration. Physical examination during the entire period of hospitalization had been negative and because of his complaints the patient had been adjudicated psychoneurotic and given a discharge from the Army after a hospital stay of 40 days for this condition. X ray films of the lungs as reported on October 13, 1942 were normal. X ray study in the hospital in Laredo also revealed normal lungs. He reported here on October 14 for the treatment of a draining pilonidal sinus. X ray examination showed a thin-

well cavitation in the left infraclavicular region whose etiology could not be determined. A repeat x-ray film on February 16, 1946, with a skin test, showed a positive reaction for coccidioidomycosis. The x-ray film of the chest in the posteroanterior view revealed a definite ring shadow in the left infraclavicular region opposite the second interspace anteriorly. There was little reaction around the shadow. The lung fields were otherwise clear and radiant. Check-up examinations at frequent intervals have shown this lesion

upper lung (Fig 4). The remainder of the lung fields were essentially normal. Extensive laboratory studies revealed a sputum analysis that was negative for tubercle bacilli and coccidioidomycosis. A skin test for coccidioidomycosis was also negative.

A closer investigation into the history revealed the fact that the patient had served from January to April, 1942, on maneuvers in southern Arizona where he had been hospitalized for an upper respiratory infection. The Mantoux test

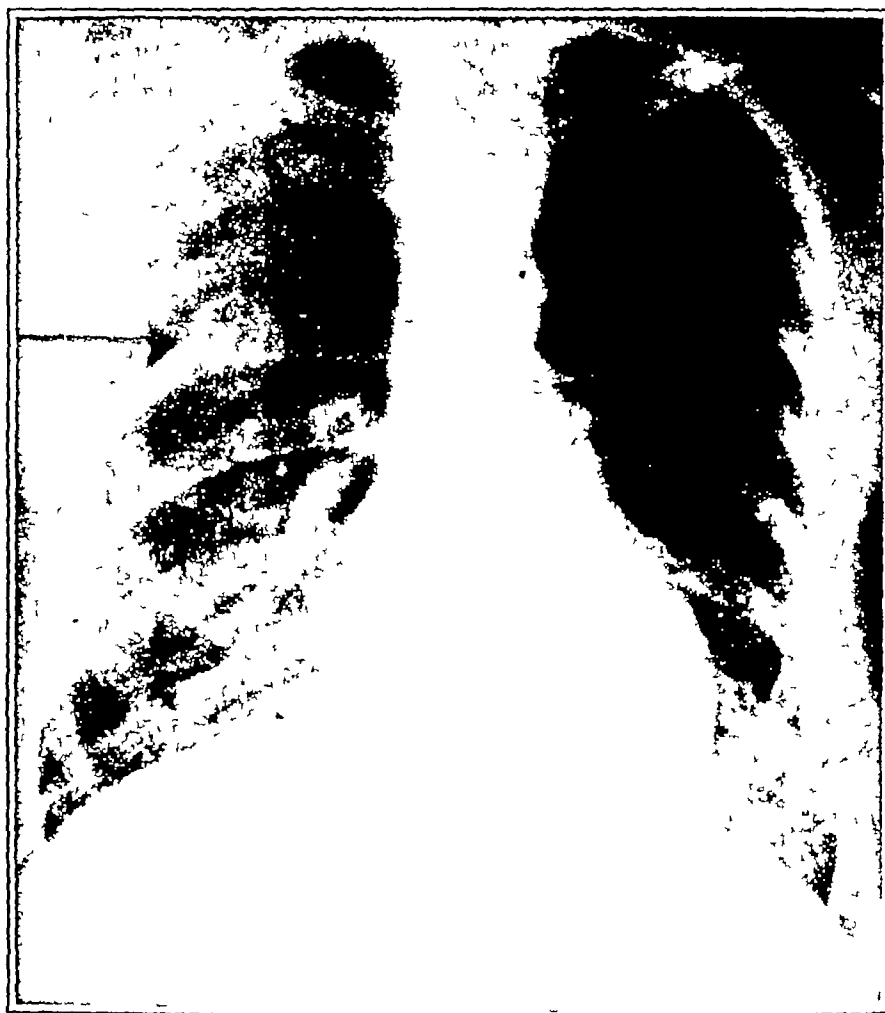


FIGURE 5 Case 3

*This roentgenogram, taken over eight months after the one illustrated in Figure 4, shows that the lesion in the right upper lobe has apparently increased in size*

to vary in size, sometimes increasing and at other times looking slightly smaller.

**CASE 3** L R B, a 34-year-old man, had served for 10 months overseas as a technician, Grade 4, in a hospital unit. In his history of service he stated that he had been hospitalized on Guam in November, 1944, because of a skin condition. This condition was diagnosed later by culture as a diphtheritic skin lesion of the left foot, which responded to 30,000 units of penicillin. He remained in service until February 10, 1945, when he was discharged. He was admitted here in August because of a chronic acne of the face and back.

Physical examination revealed an asthenic patient with a marked lymphosis. There was moderately advanced acne of the back, characterized by papulopustular lesions and marked scarring. The remainder of the physical examination was essentially negative.

Routine x-ray films of the chest taken on September 18 disclosed a well defined 1.5-by-1.5-cm cavity of the right

at this hospital was negative. The skin condition was treated here, and biopsy of the lesions of the back revealed several cysts lined with hyperplastic, squamous, stratified epithelium. The lumen was filled with desquamated, keratinized epithelium. There was intense infiltration of the adjacent tissue by polymorphonuclear leukocytes, foreign-body giant cells and lymphocytes. The diagnosis was that of multiple cholesteatoma. X-ray study on February 6, 1946, revealed the cavity of the right upper-lung field to have decreased in size; examination on June 12 showed slight enlargement of the cavitation of the right upper lobe as compared with previous x-ray findings (Fig 5).

**CASE 4** F D, a 30-year-old native of Montpelier, Vermont, was admitted to the hospital in April, 1945, for the removal of a pilonidal sinus. Routine x-ray study revealed a small cavitation, 1 cm in diameter, in the left upper lobe. Questioning disclosed that the patient had served in the

Indio Desert, California, for 8 months in 1942 but that he had had no illnesses while there.

A skin test was positive for coccidioidomycosis immittis, and the patient was carried as an additional case.

### Discussion

The 4 cases presented above were in the subsiding phase, with minimal residual evidence of the pulmonary infection in the lung. The 1 clinically active case, showing the unusual lip lesion described, also revealed only the residual ring shadow in the upper left lung (Fig 3).

The clinical course has been well correlated with the roentgenologic findings in this disease by Sweigert, Turner and Gillespie, who divide the roentgenologic manifestations of primary coccidioidomycosis as follows: pneumonitis, 70 per cent, adenitis, 23.3 per cent, cavitation, 7.8 per cent, nodules, 5.2 per cent, pleural effusion, 2.6 per cent, and normal chest, 2.6 per cent.

The pneumonitis may be slight and barely visible on the x-ray film, or multiple areas of the lung may be involved with a considerable infiltration, but the statement is made that "consolidation of an entire lobe is extremely rare." These infiltrations may resolve in one to four weeks, but usually complete resolution does not occur. There are, then, two courses: either healing and fibrosis may predominate, or cavitation results from focal necrosis in the involved lung area. The cavity may then gradually disappear, or residual scarring may persist. It is possible that the ring-like shadows demonstrated in the cases presented above were chiefly residual scarring.

Sweigert et al describe two types of cavity formation, one occurring in an area of pneumonitis with focal necrosis. "This type of cavity is quite thin-walled and is likely to be irregular in contour. These cavities frequently persist for more than a year and may vacillate in size to the extent of increasing in volume, after having decreased markedly."

One of the cases presented above (Case 3) demonstrated this feature (Fig 5). This man had had numerous chest films from December, 1944, to September, 1946, showing only a small residual nodular lesion in the film of December 3, 1944, taken in the Ninth General Hospital. The lesion was then circular and 1.5 cm in diameter, without noticeable cavitation. It increased gradually through a period of six months at Lovell General Hospital from 1.7 by 2.2 cm. to 3.0 by 2.3 cm. (six examinations from February 16 to August 28, 1945). It was in the larger phase when he entered the hospital — measuring 3.0 by 2.5 cm. on the film. All subsequent films were taken at the same distance with the patient carefully positioned so that the chest diameter was the same on all subsequent films. Again the cavity diminished from the above measurement to 1.7 by 1.3 cm. in diameter on June 3, 1946. Monthly films disclosed gradual diminution, but the film of Septem-

ber 12 again showed a slight increase, when the ring shadow measured 1.8 by 1.8 cm.

Apparently, in spite of these changes in the appearance of the pulmonary lesion, the condition was symptomatically quiescent and the patient had no complaints referable to the chest.

Adenitis, hilar and mediastinal, is a usual accompaniment, listed as 23.3 per cent but probably somewhat higher, since prominent nodes may appear in both the mediastinal and the hilar areas, subsequently returning completely to normal, with no evidence of the disseminated phase at any time.

The only case showing the nodular phase described by Sweigert et al. was also the case that demonstrated the variability of the lesions, and in that case the cavity was thin walled and somewhat irregular in outline.

None of the cases showed evidence of pleural effusion during the periods under observation at this hospital.

\* \* \*

The cases reported above revealed nothing new so far as the occurrence, geographic distribution and character of the disease are concerned. There are, however, several interesting facts that have developed — clinicians along the Atlantic Seaboard must be aware of this condition, and it may be expected to occur among personnel seen away from their previous locations. In addition, there is brought forth the urgent necessity for frequent x-ray examinations of persons who have been in areas endemic for coccidioidomycosis, skin lesions developing in such people, particularly of a granulomatous nature, should be carefully studied for the presence of the fungi.

From the standpoint of differential diagnosis, if coccidioidomycosis is kept in mind and histories of the possibility of exposure are carefully taken, there should be no difficulty in separating these cases from tuberculous infections, particularly in the late stages that are likely to be picked up in this community. The ring shadows are fairly sharply defined, and there is no reaction around them. There are no "flaky" or hazy shadows in the surrounding lung parenchyma, and in this limited series the lesions were solitary, without other reaction in the chest.

Metastatic cancer and bronchiogenic carcinoma may also be simulated, but the multiple lesions in the former and the absence of atelectatic areas in coccidioidomycosis should serve as differential features. Positive skin and serologic tests help to confirm the radiographic findings.

Lastly, the case with the skin lesion represents a decided cure under x-ray therapy, and the advantageousness of this therapy is well illustrated by the intractability of the lesions to all other recognized forms of therapy, such as the sulfonamides, penicillin, streptomycin and the iodides.

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## PSYCHOTHERAPY IN GENERAL MEDICINE\*

## Report of an Experimental Teaching Unit on a One-Hundred-Bed Medical Service

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IT HAS now become generally recognized that in some way must be found to teach medical students and house officers the kind of personal therapy that has always been carried out by the family physician without his even being aware of the fact that he was doing anything unusual. Modern conditions of medical practice, with increasing emphasis on specialization and with the growth of large urban medical centers, have made it increasingly difficult for patients to be understood in terms of personal history in a family setting. The discoveries of psychiatry during the course of the past fifty years concerning the psychology and the physiology of the emotions have become so well established that it is no longer fair to the young physician or to his future patients to send him out into practice without carefully planned instruction along these lines. The whole question of what to teach and how to go about it has become a matter of general concern, especially since the experiences of the recent war have emphasized the importance of psychologic factors as a cause of disability among large numbers of supposedly healthy young men and women.

## General Organization

To supplement the regular instruction in psychiatry along these lines the Departments of Medicine and Psychiatry at Harvard Medical School have established a special medicopsychiatric teaching unit, which has been in operation for over a

year at the Peter Bent Brigham Hospital. The general organization of this unit is presented in Figure 1. The purpose has been to demonstrate methods of psychologic treatment appropriate to the care of patients admitted to general-hospital wards because of illnesses requiring medical or surgical supervision. Special emphasis has been placed on working out a program for teaching the emotional factors in medical practice to third-year and fourth-year medical students, as well as to the house staff of the Peter Bent Brigham Hospital. The unit has functioned as an integral part of the Medical Service, and the relation of members of the unit to the medical house staff has been that of consultants. Clinical responsibility for patients admitted to the hospital has been left in the hands of the medical staff, and house officers have been encouraged to make use of psychiatric consultations to give them a better understanding of the patient and to stimulate interest in the personal factors affecting the illness. Establishment of a separate psychiatric service was carefully avoided, since this would have made it too easy for the house staff to turn over patients with any sort of emotional problems to someone else instead of working with these factors along with the manifestations of physical disease. It was found that many of the patients with clearly demonstrable organic abnormalities were as much disabled because of their emotional reaction as they were because of the disease that had provided their ticket of admission to a medical or a surgical service.

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There were also many patients presenting difficult diagnostic problems that could be solved only by a careful consideration of the psychologic data. Finally, there were cases of duodenal ulcer, mucous colitis, asthma, hypertension, hyperthyroidism and various other clinical entities in which the importance of the emotional factor has been generally accepted.

Selected patients have been treated by members of the unit during a series of outpatient interviews following discharge from the hospital. The therapeutic results have been used to illustrate the role of the specialist in the treatment of general medical cases. It has been the policy of the unit to work particularly with patients of a type likely to consult

such a way as to bring out the importance of family relationships, the role of anxiety as an expression of powerful internal conflicts in contrast to more specific fears related to real dangers in the objective world and finally the bearing of both family relationships and neurotic anxieties on the therapeutic possibilities of the patient-physician relation. During the past year the teaching program has been planned especially for third-year and fourth-year students at Harvard Medical School and for members of the medical house staff.

#### *Teaching of Fourth-Year Medical Students*

Fourth-year students at Harvard Medical School are assigned to the Peter Bent Brigham Hospital for

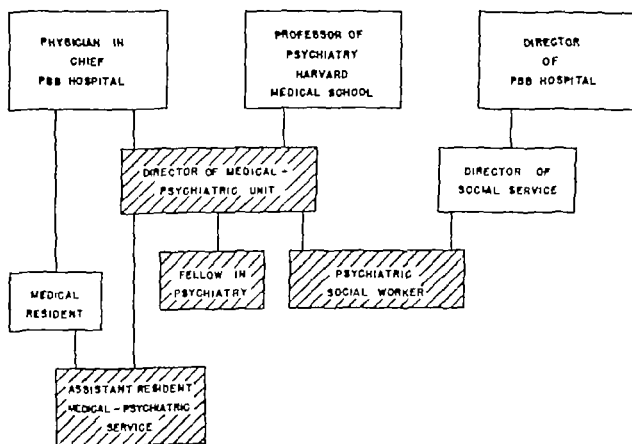


FIGURE 1 *Chart of Organization*

a general internist or a general surgeon and to share psychiatric training with internists and surgeons, who will themselves have to handle many of the patients presenting psychologic problems. Even if it were possible to refer a far greater number of patients to psychiatric specialists, it seems highly desirable for all physicians to acquire a much greater understanding of the psychology of their patients than most of them now possess. The unit has therefore directed its efforts toward the demonstration of improved methods for the handling of patients in the general medical and surgical situations, and the nature of the more fundamental make-up of the patient has also been brought out to provide a better understanding of the way in which long-standing emotional patterns contribute to the production of current symptoms.

It has been found desirable to organize case presentations at clinics and for student conferences in

their medical work over a period of two or three months. There are usually six to eight students on the Medical Service at one time. The students are seen by the staff of the unit for teaching conferences three times a week. One day, each week, the students gather for a seminar discussion of some general topic, such as the technic of the interview, anxiety as an expression of internal conflict, the bearing of family relationships on illness, the emotional implications of chronic disease, the evaluation of suicidal risk on a general medical or surgical service, discussion of psychiatric referral with illustrations of psychotherapy as carried out by the specialist, the use of psychiatric and general medical social service or various phases of normal emotional development, including particularly the general problems associated with adolescence, choice of vocation, marriage and retirement. In addition, a second hour is devoted on another day to the pres-



entation of a current case from the Medical or Surgical Service. Each of these patients has been seen at least two or three times by one of the staff of the unit so as to make sure that the relevant psychologic material is available for discussion and demonstration. Active participation in the discussion by the students has been achieved without much difficulty.

After the first few months, it was found desirable to add to this program a third hour, which is now considered perhaps the most important of all. This consists of a private conference each week for each student with the director of the medicopsychiatric unit. Each student is thus interviewed alone anywhere from eight to twelve times during his service on the medical wards. These conferences are made as flexible as possible so as to allow the student not only to discuss the facts of the cases he is attempting to handle but also to talk over whatever personal difficulties he may have with the patient-physician relation. It has thus been possible to work out some of the personal difficulties that lead students to resist discussion of emotional or psychologic data. One student, for example, was having considerable difficulty relating his interest in the emotional problems of his patients to his own strict and highly intellectualized Roman Catholicism. He expressed himself as feeling personally much more at ease after the conclusion of his three months on the Medical Service, and his ability to work with a wide variety of patients was, he believed, considerably enhanced. Another student was puzzled over his destructive impatience when taking a history of boys from the ages of fourteen to eighteen. After a few discussions of his own emancipation problem, he reported that he was having no difficulty in dealing with the boys assigned to him, and his general capacity for working with all sorts of patients was quite noticeably improved. We were much encouraged to find that ever since the institution of this third hour we have had 100 per cent attendance at all clinics and seminars.

#### *Teaching of Third-Year Medical Students*

Third-year students at Harvard Medical School are assigned to the Peter Bent Brigham Hospital for a period of twelve weeks. They usually come in two groups of four to six each. The medical teaching program includes training in the taking of histories and the performance of physical examinations followed by work with a series of patients for a week at a time. Each student thus sees from eight to ten patients during his twelve weeks on the Medical Service. The medicopsychiatric unit participates in this program. Each group of four to six students is given instruction concerning the methods and content of the personal history, family relationships, anxiety as the expression of neurotic conflict and the importance of repeated interviews being stressed to establish enough of a patient-physician relation

to make it possible for personal material to be shared by the patient with the physician. This teaching conference immediately follows the two introductory sessions by the general-medical-staff members on history taking and the physical examination. In addition to this general discussion, each student is assigned to a case selected by the medicopsychiatric unit for a period of one week. The student is supervised by the psychiatric fellow or by the assistant resident of the medicopsychiatric service, and at the end of the week each student has an hour's conference with the director of the unit. It has been found that the students are highly receptive to this sort of instruction at this period when they are just beginning to interview their medical patients. This individual instruction is reinforced by clinical demonstrations and case presentations to larger groups of the third-year students. During the course of the year every member of the third-year class at Harvard Medical School attends at least two such clinical demonstrations at the amphitheater of the Peter Bent Brigham Hospital.

#### *Teaching of the House Staff*

All the assistant residents report each morning to the physician-in-chief, briefly describing the new patients who have been admitted during the previous twenty-four hours. The director of the unit has been welcomed as a participant in these morning sessions and has thus had the opportunity to indicate personality factors that may be playing a part in the diagnostic and treatment problem of patients as they enter the hospital. The wholehearted support of the physician-in-chief has been a most important influence in the establishment of the program.

The psychiatric fellow and the assistant resident of the medicopsychiatric service each have an office on one of the two largest medical wards. This has provided direct and intimate access to the patients on the ward and has also made it easy for members of the house staff to talk things over informally with members of the unit.

At the request of the physician-in-chief a more formal course was organized for the instruction of the members of the house staff. The interns were given what amounted to eight seminar sessions, which all of them attended. Each topic was illustrated by case material from patients recently admitted to the Peter Bent Brigham Hospital. The topics were as follows:

January 6, 1947 *Psychotherapy* — the use of psychologic measures in the treatment of sick people

Altering the *environment* by talking to a relative, dealing with the employer, discussion with the minister or teacher or changing the living arrangements with the help of social service

suggesting diversions, hobbies and so forth or advising a vacation

*Supportive treatment* by reassurance, physiotherapy, suggestion and the use of pharmacologic aids in the setting of the patient-physician relation

Helping the patient to *understand himself* better This ranges from providing release from emotional tensions through giving the patient an opportunity to express himself to an interested and informed but noncondemning person, to the establishment of a special relation to the therapist, which makes it possible for repressed emotions to emerge into consciousness The latter requires a carefully trained specialist.

January 7 Neurotic symptoms and various physiologic disturbances as ways of dealing with *anxiety* Realistic fears — for example, the reaction to disabling illness or old age — contrasted with neurotic anxiety arising from a dangerous conflict of forces within the personality

January 13 Growth of personality in *childhood* Influence of emotional relations to parents and siblings on habits of eating, sleeping, bowel and bladder control, and play activity at different ages Patterns of dependence and overprotection, sibling rivalries and their influence on personality development

January 14 Psychology of *adolescence* or the process of emotional emancipation from the family, psychosexual maturation ("crushes," hero worship, sex phantasies), nature of the storms and stresses in girls (menarche) and boys

January 20 *Vocational* choice, satisfaction and dissatisfaction in the setting of relations to superiors, inferiors and equals, particularly as influenced by attitudes toward authoritarian figures, personal patterns of rivalry, need for prestige and self-assertion, drive for security and reaction to responsibility

January 21 Psychology of *marriage* — biographical factors influencing the personal and sexual adjustment (Adjustment to masculine and feminine roles)

January 27 Patient-physician relation in terms of personal attitudes on the part of

The patient — especially attitudes of dependence on parental substitute, and the physician (tendency to identification with the patient — "sympathy" — or the rejection of the patient — "impatience" — because of the doctor's own conflicts)

January 28 Technique of the *interview* — maintenance of interest through nonleading questions, avoidance of argument, "throwing the ball back" to the patient, following up leads, letting patient paint his own picture and so forth

Suggested reading included *The Happy Family*, by Levy and Monroe, *The Parents' Manual*, by Anna W. M. Wolf, *Baby and Child Care*, by Benjamin Spock, and *Psychotherapy in Medical Practice*, by Maurice Levine

All the sessions were conducted by the director of the unit, except for the session on childhood Dr. Marian C. Putnam, the director of the Children's Center at Roxbury, was kind enough to give this talk.

Although the interns at first manifested an attitude of polite and rather cool skepticism, it was quite evident that as the sessions progressed their enthusiasm and active participation increased to a gratifying extent.

These seminar sessions were followed during the month of February by four sessions (one a week) with patients in the Out-Door Department under the supervision of a senior psychiatrist.\* Each psychiatrist supervised two interns an afternoon for four afternoons. Most of the interns were quite enthusiastic about this type of instruction, and all of them were interested. The psychiatrists were also quite enthusiastic. The chief difficulty encountered was the selection of patient material. This responsibility had been left to the individual house officers, and it turned out that they really needed much more guidance than we had been able to give them in this matter. Quite a number of the interns plan to follow their patients for a period of several months, and several of the psychiatrists have agreed to make themselves available for further instruction and guidance. Since the presentation of this course, there has been a noticeable alteration in the general attitude toward the work of the medicopsychiatric unit on the wards, and this has had a particularly favorable influence on the medical students, who were previously somewhat discouraged by the skepticism of the house officers.

#### *Personnel of the Unit*

The director of the unit was given an appointment in the Department of Psychiatry of Harvard Medical School, as well as an appointment on the Medical Service of the hospital. A psychiatric fellow and an assistant resident of the medicopsychiatric service have carried out psychiatric interviews on all the patients presenting emotional problems of any importance on the Medical Service, which contains one hundred beds, and they have also seen a number of patients on the Surgical Service as well. Copies of their full notes have been attached to the medical records of each patient so as to provide guidance for members of the house staff and members of the visiting staff as well. On various occasions during the course of the teaching session the members of the staff of the unit have presented the

\*We were fortunate in obtaining the co-operation of Drs. Donald J. MacPheron, Laurence D. Trevel, Frank L. d. Flaxman and John A. Abbott, all of whom are practicing psychiatrists with a strong interest in psychotherapy and an enthusiasm for individual instruction.

biographical material concerning patients who were presented at the weekly medical grand rounds attended by the students and visiting staff. These presentations have been effective in stimulating general interest in the psychologic problems of patients in the hospital. A psychiatric social worker was found to be indispensable. Although she has been able to make contact with various relevant social agencies, her more important function has been that of active participation in the handling of the more significant relatives of patients who are being treated by the physicians of the unit. It was found that a full-time secretary had all that she could do to keep up consultation notes and treatment interviews for the four members of the staff.

### *Future Planning*

It has been found during the course of the past year that effective teaching of medical students and staff can be carried out only if those who are giving the instruction have a grasp of the case material used for illustration that is considerably more profound than a beginner could expect to achieve even after a series of interviews with the patient. To give students any help in handling their patients more effectively, those who are doing the teaching must have as clear a realization as possible of the nature and therapeutic plasticity of the patient's difficulties. This not only requires considerable maturity and experience but also can be carried out with conviction and vitality only if those who are doing the teaching of beginners are at the same time in daily therapeutic contact with patients at a much more understanding level than would be possible or desirable for a student. These considerations are of particular importance when any future expansion of the present program is considered. In other words, teaching of additional medical students, members of the medical house staff, members of the visiting staff and others could be carried out usefully only with the help of mature and experienced psychiatrists who would be interested. Unsupervised teaching by beginners is quite likely to do more harm than good.

These considerations seem to apply to the problem of research along psychologic lines in the general medical field. It is our conviction that the most needed type of research is in the field of therapy, which is also the chief avenue to an understanding of fundamental etiology. Although the collaboration of colleagues versed in the discipline of physiology and biochemistry is desirable, what is most needed in the personnel undertaking such research appears to be a thorough grounding in psychiatry and psychotherapy.

### *Cost*

The unit has been housed at the Peter Bent Brigham Hospital, where office space has been assigned each member. Salaries and operating expenses amounted to \$17,000 during the first year of operation.

The distribution of salaries was according to the relative training and experience of the various members of the unit. The junior members of the staff were willing to serve for low salaries because of the opportunities for experience and teaching.

### SUMMARY

An experimental medicopsychiatric teaching unit has been in operation on a one-hundred-bed medical service at the Peter Bent Brigham Hospital for a year.

Methods of psychologic treatment appropriate to the care of patients admitted to general hospital wards are discussed.

A program for the teaching of the emotional factors in general medical practice has been established for third-year and fourth-year medical students assigned to the Medical Service.

A course for medical house officers has been presented with seminar discussions and individually supervised clinical work.

Considerations relevant to expansion of the present service are discussed, with particular regard to the requirements and opportunities of the personnel.

## PLEURODYNIA\*

## Preliminary Note on an Epidemic in Boston

JOHN J. FINN, JR., M.D.†

BOSTON

**B**EGINNING in July and continuing through August and September, 1947, a large group of patients afflicted with an acute febrile illness resembling what has been popularly known in the United States as "devil's grip" or "epidemic pleurodynia" were admitted to the medical and surgical wards of the Boston City Hospital. At the time of submission of this report, patients are still being admitted sporadically.

So far as is known, the last reported epidemic of this disease in the United States was the Brooklyn epidemic of 1942.<sup>1</sup> A smaller group of cases, consisting of 12 hospitalized and 8 nonhospitalized patients among members of the families of the hospital patients, were observed at the Boston City Hospital during the same year.<sup>2</sup>

The current epidemic appears to be of major proportions, for not only is the number of known hospitalized cases at the Boston City Hospital well over the 100 mark but also the number seen in the Outpatient Department and on the Emergency Floor and not admitted is estimated to have far exceeded this figure. Furthermore, the known nonhospitalized cases among members of the patients' families and friends, in addition to reports of cases seen at other hospitals in Boston and throughout New England, make it appear that the total number of cases of the disease must have numbered in the thousands.

If the experience at the Boston City Hospital is any criterion, it appears that the disease is being misdiagnosed in many cases and is being confused with pneumonia, influenza, infectious mononucleosis, nonparalytic poliomyelitis, lymphocytic choriomeningitis, gastroenteritis and acute surgical conditions of the abdomen. The diversity of signs and symptoms easily accounts for this confusion.

The purpose of this preliminary report is to call attention to the presence of the epidemic and its varied manifestations among the patients seen at the Boston City Hospital. The report includes a general description of the disease, with some of its less common manifestations, as well as selected case reports from the present epidemic, which will suffice to point out the diverse manifestations of this disease. The literature concerning this disease was reviewed in 1934 by Sylvester<sup>3</sup> and in 1946 by Scadding.<sup>4</sup>

A complete report of the clinical data and laboratory studies of cases seen at the Boston City Hospital during the current epidemic and the one of 1942 will be presented at a later date.

## DESCRIPTION

The disease occurs in the late summer and early fall and seems to affect mostly younger people. In general, it is characterized by lack of prodromes, the onset being sudden and the initial symptom in most cases being pain. The pain is usually located in the lower thoracic or upper abdominal regions, or both, and may vary in intensity from a dull ache or distressed tight feeling to an excruciating type. The pain is usually intimately associated with the line of attachment of the diaphragmatic insertions to the thoracic wall and is aggravated by deep breathing, by coughing and frequently by motion. There is usually an associated hyperesthesia in the areas of distribution of the pain, which tends to occur in paroxysms. It may shift from one side of the thorax to the other but is usually located in the region of the diaphragmatic attachments. Shoulder, scapular or interscapular reference of the pain may occur. Soon after or coincident with the onset of pain, there is fever, the temperature reaching as high as 104°F in a few hours (usually about twelve hours), with a gradual fall to normal within the next twelve hours. After the initial return of the temperature to normal, there may be one or more recrudescences of pain and other symptoms. Between recrudescences, the patient may be completely asymptomatic. Once the fever has permanently remitted there are usually no further symptoms except for an occasional twinge of pleurodynia. The fever, however, may run an irregular course up to ten to fourteen days. Chills or chilly sensations are not uncommon and may be the initial symptom. Other symptoms described in previous epidemics include mild upper respiratory symptoms, such as a so-called "head cold," mild pharyngitis and slight, nonproductive cough; central-nervous-system symptoms such as headache, which may be severe, photophobia, paresthesias and even convulsions, and gastrointestinal symptoms, such as anorexia, nausea, vomiting, diarrhea and tympanites, especially in children. Physical findings in the usual case are rather few other than the fever, splinting of the chest and upper abdominal or thoracic tenderness. A pleural friction rub may or may not be heard at

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some time during the course of the disease or even in convalescence. X-ray films of the chest are classically completely normal. Laboratory studies are of little significance. The white-cell count is normal or slightly elevated at the beginning of the illness, with a drop later. Eosinophilia, especially in convalescence, has been described in earlier epidemics. The disease is apparently a benign one in the vast majority of cases, although complications such as pericarditis, orchitis and jaundice have been mentioned.

The cause of the disease is unknown, the general impression being that it is of viral origin with an incubation period of eight to ten days.

### CASE REPORTS FROM THE CURRENT EPIDEMIC

The diversity of signs and symptoms of the disease as seen in the present epidemic is best illustrated by the following selected cases. The first illustrates the clinical course of a typical case and the high household incidence of the disease.

**CASE 1** A 44-year-old man entered the hospital on July 28, 1947, because of chest pain, fever, vomiting and chilliness. He had been well until a few hours before admission, when he had noted chilly sensations, and shortly thereafter he had been seized with a sharp vise-like pain around the entire lower thorax. The pain was aggravated by respiration and radiated to both shoulders and to the interscapular region. In addition, the patient vomited and noted a "burning" sensation of both eyes.

Physical examination revealed slight conjunctival injection, a few nontender palpable cervical lymph nodes, splinting of the right half of the chest and tenderness to palpation over the lower thorax and upper abdomen bilaterally.

The temperature was 103.6°F, the pulse 112, and the respirations 40. The blood pressure was 110/70.

Examination of the urine, and cultures of the nose, throat and blood were negative. Examination of the blood disclosed a white-cell count of 17,600, with 80 per cent neutrophils and 20 per cent lymphocytes. The sedimentation rate was normal, as were an x-ray film of the chest and an electrocardiogram. The white-cell count fell to 6800, with an essentially normal differential count, on the 4th day, and on the 7th day it was 12,000, with 69 per cent neutrophils, 25 per cent lymphocytes and 6 per cent eosinophils. Treatment consisted of intramuscular penicillin and Demerol. Within 24 hours after admission the temperature had returned to normal, remaining so for 48 hours, when there was a recrudescence to 102°F and a return to normal within 24 hours, only to be followed 72 hours later by a final rise to 99.8°F. A pleural friction rub was heard over the right lower posterior portion of the chest on the 7th day, and on the 10th day it was heard bilaterally over the lower portion of the chest anteriorly and posteriorly, and was still present, although the patient was asymptomatic, when he was discharged on August 7.

Five other members of the patient's family and 3 people living in the tenement below became ill, with similar symptoms, either a few days before or a few days after the patient's illness had begun.

The following case illustrates the central-nervous-system involvement and a rather common hematologic picture.

**CASE 2** A 21-year-old woman entered the hospital on July 29, 1947. She had had a mild diarrhea 4 days prior to entry, and on the following day awoke with a severe pain in the upper epigastrium, radiating to the neck and ears and aggravated by respiration. The pain was accompanied by malaise, fever, chilly sensations and severe headache. For the next 3 days there were daily recurrences of all symptoms,

and the pain became localized first to the left lower lateral portion of the chest and then to the right lower lateral portion, and was referred to the right shoulder and scapular area.

Physical examination showed a somewhat drowsy patient, with slight pharyngeal injection, a few palpable axillary and inguinal lymph nodes, moderate tenderness to palpation over the lower part of the sternum, right lower lateral portion of the chest and right costovertebral region and tenderness to deep pressure in both calves.

The temperature was 103.8°F, the pulse 104, and the respirations 24.

Cultures of the blood, throat and feces and examination of the urine were negative. Examination of the blood revealed a white-cell count of 3600, with 57 per cent neutrophils, 41 per cent lymphocytes, 4 per cent monocytes, 1 per cent basophils and 8 per cent atypical lymphocytes. X-ray films of the chest and an electrocardiogram were normal. On the 8th day the white-cell count was 7300, with 55 per cent neutrophils, 32 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophils and 8 per cent atypical lymphocytes. Heterophil-antibody agglutinations done on the 1st, 4th and 7th hospital days were all negative. The spinal fluid on admission showed 22 white cells per cubic millimeter, of which 18 were lymphocytes, 2 were neutrophils and 2 were monocytes. Culture of the spinal fluid showed no growth, and the chemical and serologic findings were normal.

The patient received intramuscular penicillin therapy during the first few hospital days. Within 24 hours after admission, the temperature had dropped to normal only to rise again to 104°F 12 hours later. There were two subsequent temperature rises to 102 and 103°F, respectively, at approximately 24-hour intervals. By the 5th hospital day the patient was afebrile and remained so. During the first few hospital days a moderate enlargement of the axillary and inguinal lymph nodes was noted, but the spleen and liver did not become enlarged. A pleural friction rub, first heard in the posterior axillary line of the right lower portion of the chest on the 5th hospital day, was still present when the patient was discharged asymptomatic on August 7.

The last case illustrates the possible confusion of the disease with acute surgical conditions of the abdomen.

**CASE 3** An 11-year-old boy was admitted to the hospital on September 7, 1947. Three days prior to entry he had noticed the sudden onset of periumbilical pain and a temperature of 101°F. Within a few hours all symptoms disappeared until the day of entry, when once again there was a recurrence of the fever and of the pain, which was aggravated by respiration and felt also in the left lower anterior portion of the chest and in the anterior part of the neck just below the thyroid cartilage.

Physical examination revealed rapid and shallow breathing, with obvious splinting of the chest and abdomen. A questionable pleural friction rub was heard in the right lower lateral portion of the chest, and there were slight tenderness and spasm in the upper abdomen.

The temperature was 102.4°F and the pulse 80. Examination of the urine, a blood culture and heterophil-antibody tests were negative. Examination of the blood disclosed a white-cell count of 13,150. The sedimentation rate, an x-ray film of the chest and an electrocardiogram were normal. On the next day the white-cell count was 3800, with 38 per cent neutrophils, 4 per cent monocytes, 1 per cent basophils, 1 per cent eosinophils and 52 per cent lymphocytes, many of which were immature.

The patient had been admitted to a surgical ward for surgical observation, but operation was not performed. Within 24 hours after admission, the temperature had dropped to normal, and the patient had become completely asymptomatic and remained so. About 72 hours after admission, however, the temperature rose to 100.5°F but rapidly returned to normal, where it remained. He was discharged asymptomatic on August 13.

At follow-up study on August 22 physical examination was negative, and blood studies showed a normal sedimentation rate, a negative heterophil-antibody test and a white cell

count of 9050, with 57 per cent neutrophils, 34 per cent lymphocytes and 8 per cent eosinophils. The patient's mother stated that a younger brother had become ill with similar symptoms the day after the patient had been admitted to the hospital.

### SUMMARY

An epidemic of "devil's grip" or "epidemic pleurodynia" occurring in Boston during July, August and September, 1947, is reported.

The epidemic appears to have been of major proportion throughout Boston and elsewhere in New England, with over 100 cases admitted to the Boston City Hospital alone.

A general description of the disease and some of its diverse manifestations is presented, and three selected, illustrative case reports from the current epidemic are submitted.

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## MEDICAL PROGRESS

### NEUROLOGY

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**PHYSIOLOGIC** studies of significance in 1946 include the reports on the effect of di-iso-propyl-fluorophosphate on transmission of the nerve impulse and the effect of this compound on the symptoms of myasthenia gravis. The poor results obtained with the use of di-iso-propylfluorophosphate in patients with myasthenia gravis, although there was a great decrease in plasma cholinesterase, suggest that the therapeutic effect of neostigmine in this disease is not related to its effect on the cholinesterase.

Important clinical studies were made on diseases of the cerebral blood vessels, the measurement of sympathetic activity in nerve injuries by the dermatometer and the treatment of infections of the nervous system with streptomycin and penicillin. Several reports indicate that streptomycin is highly effective in the treatment of meningitis caused by *Haemophilus influenzae*. It has a definite effect on the course of tuberculous meningitis, prolonging life without effecting a cure in the majority of cases in which it has been used. Further reports on the results obtained with the use of penicillin in the therapy of neurosyphilis suggest that this antibiotic will ultimately replace the older, laborious and more dangerous forms of therapy in this disease.

The studies mentioned above, together with numerous others, are considered under the following headings: physiology, cerebral blood vessels, nerve injuries and skin-resistance tests, infections, convulsive disorders, and miscellaneous considerations.

### PHYSIOLOGY

In the course of chemical-warfare research, it was found that di-iso-propylfluorophosphate (DFP) seemed to act as an "irreversible" inhibitor of cholinesterase and thus apparently to set up the possibility of a direct, crucial test of the importance of the acetylcholine system to propagation of nerve impulses. Crescetti, Koelle and Gilman,<sup>1</sup> in experiments with the sciatic nerve of bullfrogs, found that the action potential was abolished by the application of DFP but reappeared on removal of the nerve from the compound. After the injection of frogs with DFP, only traces of cholinesterase activity were found in the excised nerves, which nevertheless had conduction properties similar to those of control fibers. From these experiments, it was concluded that there is no parallel between the magnitude of the action potential and the cholinesterase activity.

Nachmansohn and his collaborators<sup>2-4</sup> have criticized certain technical aspects, as well as the conclusions, of this work, offering several experiments in rebuttal. In manometric studies with cholinesterase and by experiments on lobsters and squid nerve, these workers have shown that the inhibiting action of DFP is not immediately irreversible, but that the irreversibility of the action depends on the time of exposure of the enzyme to the drug and on the temperature. The time independence of the inactivation was used to demonstrate that progressive irreversible depression of the action potential was paralleled by a progressive decrease in available cholinesterase. Similarly, it was found that com-

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plete return of the action potential in these nerves is always accompanied by the presence of at least 20 per cent of the initial cholinesterase

In evaluating these and similar experiments, Grundfest<sup>6</sup> came to the following conclusion "Whatever its specific role may be, the acetylcholine system enters into the activity of excitable conductile tissue at a more crucial stage than do, for example, oxygen and other metabolic systems"

Two studies have appeared on the effects of DFP in normal subjects and in patients with myasthenia gravis. Comroe and his associates<sup>7</sup> found a marked reduction in plasma cholinesterase activity and a slight reduction of red-cell cholinesterase in normal persons after the administration of DFP in doses of 0.7 to 3.0 mg intramuscularly and 2.5 to 10.0 mg orally. Single intramuscular injections in normal subjects had no effect on pulse, blood pressure, electrocardiogram, vital capacity or blood sugars. In 7 patients with myasthenia gravis comparison was made of the effectiveness of DFP with that of neostigmine in the relief of weakness and in the correction of abnormal electromyogram characteristics. DFP, in doses of 2.5 to 210 mg given over periods of one to one hundred and fifty days, was longer lasting in its effect than neostigmine but did not produce so great an increase in strength. DFP decreased plasma cholinesterase activity to 1 to 10 per cent of normal, with only partial improvement of strength, whereas neostigmine produced marked increase of strength with decrease of plasma cholinesterase activity to only 50 to 70 per cent of normal. Thus, it appears that the efficiency of drugs in the treatment of myasthenia gravis cannot be determined by their effects on plasma cholinesterase. Toxic symptoms that result from the use of this compound include anxiety and disturbing dreams, and abnormalities may develop in the electroencephalogram.

In a second series of observations, Harvey et al.<sup>8</sup> compared the results of the injection of 1.5 mg of DFP in physiologic saline solution into the brachial arteries of normal and myasthenic subjects. In the former, fasciculations and weakness developed in the muscles supplied by this artery, whereas in the latter there were no fasciculations and there was an increase in strength of eight to ten days' duration in muscles supplied by the artery, with restoration of normal electromyographs.

It was a dictum of Hughlings Jackson that movements, not muscles, are represented in the motor cortex, whereas Sherrington developed a theory of punctate localization of cortical motor function. Hsiang-Tung Chang, Ruch and Ward,<sup>9</sup> in the light of these differing views, have investigated the topographic representation in the motor cortex of individual muscles acting over the ankle joint of macaque monkeys. Not only individual muscles but also slips of muscles were found to have a focal point in the cortex from which an isolated response of that muscle or muscle slip is elicitable or at which the re-

sponse is stronger and prompter, in relation to other muscles.

Lloyd<sup>10</sup> has continued his studies of the functional organization of the spinal cord with an investigation of events at the synapse in a 2-neuron arc. He finds evidence that three events take place at the synapse. The first is a brief, powerful component of the excitatory event, capable of adequate stimulation of the neuron and already well known as the "detonator action." The second is another component of excitation of longer duration than the first, not so powerful, capable of facilitating the "detonator action," but not in itself capable of discharging a neuron. Lloyd calls this "residual facilitation." The third event, an inhibitory process, is considered the functional opposite of "residual facilitation," on the basis of its characteristics of temporal delay. In a broader study Lloyd<sup>11</sup> investigated the relation of these phenomena to the integrative pattern of the spinal cord and showed that without the necessity of other than direct reflex connections, the myotatic unit exhibits, complete within itself, the elementary mechanism of reciprocal innervation.

Lennox and Ruch<sup>12</sup> have developed a technic in monkeys for recording the electrical activity of the brain by means of wire electrodes inserted into the ventricles. They have suggested that the method is applicable to human beings in conjunction with ventriculography and believe that by its use, it may be possible to lateralize deep subcortical lesions and to demonstrate the subcortical origin of various abnormal waves.

#### CEREBRAL BLOOD VESSELS

Kubik and Adams<sup>13</sup> have analyzed the clinical and pathological manifestations in 18 cases of occlusion of the basilar artery. This finding has been observed at autopsy in 1,300 cases at the Massachusetts General Hospital and the Mallory Institute of Pathology. The occlusion was thrombotic in 11 of 18 cases, and embolic in the remaining 7. The symptoms and signs were found to fit a rather definite pattern, characterized by abrupt onset and changes in state of consciousness varying from confusion to coma, with headaches, dysarthria and dysphagia, pupillary abnormalities, ocular and facial palsies, hemiplegia or quadriplegias, bilateral extensor plantar responses and often a terminal hyperpyrexia. In some cases there was a temporary remission, followed in fatal cases by relapse and death. The cerebrospinal fluid was clear and under normal pressure. The authors also state that they have seen 7 patients who recovered after the occurrence of signs and symptoms resembling those of basilar-artery occlusion.

Madonick, Savitsky and Hochfeld<sup>14</sup> reported a patient dying with a subarachnoid hemorrhage from an intracranial aneurysm associated with polycystic kidneys in whom these findings were verified at necropsy. They described another patient who had

two episodes of subarachnoid bleeding and in whom intravenous urography revealed signs of polycystic kidneys. They also found in the literature 13 cases of verified intracranial aneurysm accompanied by polycystic kidneys.

A series of 15 patients in whom vascular anomalies of the cerebral cortex were present in association with Jacksonian epilepsy has been reported by Reichert.<sup>14</sup> Surgical treatment, consisting in coagulations of the vascular lesions, resulted in the disappearance of attacks in 6 cases, milder and less frequent seizures in 7 and no improvement in 2.

Kilbourne and Wolff<sup>15</sup> have studied 21 cases of temporal arteritis, which they conclude is a well defined pathologic entity. It characteristically occurs in patients of both sexes between the ages of fifty-five and eighty, with painful inflammation of one or both temporal arteries as the main symptom. Usually present are the findings of a mild systemic infection, with leukocytosis but without eosinophilia. Koch's postulates have not been fulfilled for any causative organism, and the authors discuss the possibility of an allergic etiology. Ocular symptoms appeared in 7 cases, ranging from photophobia and diplopia to blindness. Four patients showed lethargy and mental retardation suggestive of encephalitis. Complete recovery took place in all patients within two to twenty months, except for blindness, which persisted when it occurred, and except for a patient who remained mentally retarded. Pathological findings in temporal-artery biopsies are indistinguishable from those of periarthritis nodosa, but the authors point out that the nonfatal course and absence of visceral involvement in temporal arteritis serve to differentiate it from periarthritis nodosa. Because of signs of involvement in many cranial arterial branches in this disease, it is suggested that it be called "cranial arteritis."

In a review of experience with cerebral angiography by means of thorium dioxide at the University of Pennsylvania Hospital, Govons and Grant<sup>17</sup> state that they have found the procedure of value in the localization of intracranial aneurysms, angiomatous malformations of the brain, occlusions of the internal carotid artery and traumatic arteriovenous aneurysms. They believe that pneumoencephalography is still the mechanical technic of choice for the localization of cerebral neoplasms.

#### NERVE INJURIES AND SKIN-RESISTANCE TESTS

Richter<sup>18</sup> has summarized information concerning the use of his dermatometer — a device that measures the relative electrical resistance of the skin. The model he has introduced consists of a microammeter, potential divider,  $4\frac{1}{2}$  volt battery, and two electrodes, one indifferent for attachment to the ear, and the other for exploration. This instrument affords a relative, but not quantitative, measure of skin resistance. Resistance to the passage of a minute direct current, imperceptible to the subject,

is localized to the skin, and is controlled largely through sympathetic fibers that govern the activity of sweat glands. The activity of these glands, in turn, determines to a first approximation the degree of skin resistance. Under ordinary conditions normally innervated skin shows distinct regions where resistance is high, and others where it is low. In general, areas of low resistance are found when there is a rich sweat-gland supply, such as the palms of the hands, the soles of the feet, the center part of the face, the axillae and the antecubital fossae. Section of a nerve trunk or removal of sympathetic supply to an area by ganglionectomy markedly increases skin resistance in the area supplied by these structures. Stimulation or irritation, on the other hand, of nerve or sympathetic chain decreases resistance. Transection of the cord at the first thoracic segment, above the thoracolumbar outflow, increases skin resistance over the head, trunk and extremities. Transection at the second lumbar segment, below the outflow, has no effect on resistance, whereas that within the outflow increases resistance of the skin supplied by the spinal-cord segments below the lesion.

The dermatometer has proved useful in the diagnosis of peripheral-nerve injury, particularly in distinguishing between complete and partial sections, in determining the earliest signs of regeneration of sympathetic fibers, in determining the rate of regeneration of sympathetic fibers with relation to sensory and motor fiber regeneration, in studying the distribution of the sympathetic component of each of the peripheral nerves separately and in combination and in ascertaining actual nerve injury in suspected cases of malingering.<sup>19, 20</sup> It has also been valuable as an aid in the diagnosis of injury or irritation to the sympathetic system, as in brachial-plexus pressure, as well as in mapping areas of skin denervation by sympathetomy, or procaine paravertebral blocks of sympathetic nerves, and finally as a help in the localizing of the level of injury to the spinal cord or roots.

Several papers have described the value of sympathetomy in the treatment of causalgia. Ulmer and Mayfield,<sup>21</sup> in a review of 72 cases of causalgia due to war wounds of large mixed peripheral nerves, state that 63 of 70 patients were relieved of pain by the first operation consisting of sympathetomy in appropriate areas of the sympathetic chain. Two patients were successfully treated by resection of the injured nerve segment.

Rasmussen and Freedman<sup>22</sup> report relief of pain in 28 of 35 cases by surgical sympathetomy for causalgia of the arm, with less satisfactory results for causalgia of the leg. Similarly, White<sup>23</sup> has reported success with this type of procedure in treatment of causalgia.

Schlesinger<sup>24</sup> has described the use of a suspension of curamine in oil and wax for the relaxation of spasticity following injury of the spinal cord. With



doses of 1.0 to 1.5 cc of curarine in oil, he found that relaxation occurred lasting as long as three days, without concomitant appearance of undesirable side effects. The emergence of voluntary function apparently masked by spasticity and the relaxation of muscle spasm, thus permitting physiotherapeutic procedures to be instituted, seemed to be of value in 11 patients treated in this manner.

### INFECTIONS

A number of reports have appeared on the use of streptomycin in infections of the nervous system due to gram-negative and acid-fast organisms.

In a comprehensive paper on the use of streptomycin, the Committee on Chemotherapeutics of the National Research Council<sup>24</sup> reports 100 cases of meningitis caused by *H. influenzae* and treated with this drug. Of these, 66 patients were cured clinically and bacteriologically while under treatment, 13 improved and finally recovered, 1 improved but relapsed, 3 showed no effect, and 17 died. Only 18 patients were treated by streptomycin alone. Analysis of the 17 fatal cases demonstrated that the factor most unfavorable for streptomycin treatment is late use of the drug after other forms of therapy have failed. In this connection, the report calls attention to the favorable results reported by Weinstein,<sup>25</sup> which suggest that early diagnosis and prompt intramuscular and intrathecal injection of streptomycin are usually followed by prompt improvement. Weinstein also stresses the occurrence of superinfections due to other organisms, such as the staphylococcus, that are resistant to streptomycin but may be sensitive to penicillin.

Although more streptomycin is present in the cerebrospinal fluid of patients with meningitis than the small amount appearing in the spinal fluid of non-meningitic patients after parenteral administration of the drug, the Council recommends intrathecal as well as intramuscular routes of dosage in meningitis therapy. The average daily dose given to the patients in the series who recovered was 0.5 gm intramuscularly, and 0.060 gm in 5 to 10 cc of physiologic saline solution intrathecally, for nine and seven days respectively.

The Council also reports a group of 14 cases of meningitis caused by gram-negative organism other than *H. influenzae* but concludes that the series is too small for satisfactory analysis.

Alexander and her associates,<sup>26</sup> after treating 25 patients with influenzal meningitis with streptomycin alone or along with other agents, state that streptomycin therapy alone will bring about recovery when the meningitis is of average severity, but that when the infection is unusually severe, therapeutic failure will probably be reduced to a minimum by the initial use of rabbit antiserum, sulfadiazine and streptomycin.

Hinshaw, Feldman and Pfuetze<sup>27</sup> describe 11 patients with milary tuberculosis and tuberculous in-

volvement of the central nervous system treated with streptomycin. Four of 9 patients so treated, who had tuberculous meningitis as proved by the clinical picture, spinal-fluid abnormalities and demonstration of the tubercle bacillus, have survived for five to ten months, although the cerebrospinal-fluid abnormalities persisted. The authors also emphasize the value of both intrathecal and intramuscular administration of the drug, stating that in their series no patient who has had intrathecal as well as intramuscular therapy has died of tuberculous meningitis.

More information on the use of penicillin in the treatment of neurosyphilis is available. Stokes and Steiger<sup>28</sup> have described the results of penicillin alone in 283 patients with neurosyphilis. The routes of administration and dosage varied widely, and many of the patients were treated during the period of high variability of potency of penicillin supplies. They recommend at present a course of not less than 4,800,000 units in not less than seven and a half days, around the clock, penicillin being used in physiologic saline solution intramuscularly. Improvement in the spinal fluid was found in 62 per cent of patients with dementia paralytica, 57 per cent with tabes dorsalis, 60 per cent with asymptomatic involvement and 63 per cent with congenital syphilis. Clinical improvement was claimed for 30 per cent of patients with dementia paralytica, 31 per cent with tabes dorsalis and 17 per cent with meningovascular neurosyphilis. The results with primary optic atrophy were considered inconclusive.

Jones and Perk<sup>29</sup> report 6 cases of dementia paralytica treated with two courses of 2,400,000 units of penicillin separated by a month. Three patients were considered improved clinically, 1 was unchanged, and 2 became progressively worse. In all cases there was improvement in the spinal fluid, a reduction in the cell count usually occurring first.

Nelson and Moore<sup>30</sup> have reported the results of an additional year of observation of 10 patients treated with penicillin for acute syphilitic meningitis and previously reported. In all 10 cases the spinal-fluid reaction, originally strongly positive, has become negative. Because of the excellent results with penicillin given intramuscularly in this form of neurosyphilis, the authors believe that it is not necessary to give penicillin intrathecally in treatment.

Callaway and his associates<sup>31</sup> have treated 2 cases of syphilitic arachnoiditis with subarachnoid block by 4,000,000 units of penicillin intramuscularly and intrathecally, and report improvement as occurring in contrast with unfavorable results with other modes of therapy.

Reports on toxicity of antibiotics for the central nervous system have appeared. Brown and Hinshaw<sup>32</sup> have reported dizziness, tinnitus and even loss of hearing as occurring in patients treated for

tuberculosis in large doses over long periods with streptomycin

Johnson et al.<sup>33</sup> investigated the effects of several antibiotics on the nervous system. Both penicillin and streptomycin produced convulsions when applied directly to the cerebral cortex. Although a fairly wide margin of safety was observed between the effective antibiotic concentrations and the convulsive concentration, the authors warn against direct exposure of the nervous system to excessive dosage of the drugs. During systemic administration of penicillin for non-neural disease, 60 per cent of patients were found to have abnormal encephalograms.

Sachs,<sup>34</sup> in a review of his experience with 142 cases of brain abscess seen during the past thirty years, concludes that no unencapsulated abscess should be drained, that penicillin during the acute stage is an invaluable aid in bringing about encapsulation, that aspiration, except in cerebellar cases, should be used only as a palliative procedure until more radical treatment can be instituted and, finally, that excision without drainage is the ideal procedure.

Five cases of radical total dissection of brain abscesses, aided by sulfonamide and penicillin therapy, have been reported by Fincher.<sup>35</sup> He states that his results with this method suggest that the basic surgical principle of "incision and drainage" in the treatment of certain abscesses of the brain can be replaced by total dissection of the abscess and primary closure of the wound.

Bronson<sup>36</sup> has reviewed a neurologic syndrome occurring among members of the armed forces that was characterized by varying degrees of disturbance ranging from mild peripheral neuritis to severe debility "involving the central nervous system as well as the peripheral nerves, similar to the Guillain-Barré syndrome." Out of 60 such patients at an Army hospital, the syndrome was found to follow cutaneous diphtheria in 5, faucial diphtheria in 2 and a severe sore throat thought to be diphtheritic in 5 others. In the remaining 48 cases, as well as in 13 patients with a similar syndrome in Australia, there was no evidence of diphtheritic involvement.

Gaskill and Korb<sup>37</sup> have described a small epidemic of cutaneous diphtheria striking 140 patients, in 61 of whom multiple neuritis developed. The authors found evidence in their study that early administration of diphtheria antitoxin in adequate doses significantly reduces the incidence of this complication.

Involvement of the central nervous system in Asiatic schistosomiasis has been reviewed by Cutter.<sup>38</sup> This frequently manifests itself with the symptoms of a space-occupying brain or cord lesion. The importance of early treatment is emphasized by the author.

Winkenwerder and his associates<sup>39</sup> have reported a series of 364 cases of Asiatic schistosomiasis, emphasizing particularly the value of Fuadin, an antimony-containing compound, in the treatment of this condition.

### CONVULSIVE DISORDERS

In a study of biochemical changes induced by convulsant drugs in the cortex of the cat, Klein and Olsen<sup>40</sup> observed decreased concentrations of brain glycogen, glucose, phosphocreatine and adenosine triphosphate as a result of convulsive activity, whereas there were increased concentrations of lactate, adenosine diphosphate and inorganic phosphate. They conclude that the cerebral metabolism of glucose is markedly increased during convulsive activity.

Perlstein and Andelman<sup>41</sup> have reported on the use of tridione in convulsive and other disorders. They found dramatic improvement in 6 of 7 patients with petit-mal epilepsy after the administration of the drug. Tridione afforded marked benefit in 3 patients with psychomotor attacks. Results in patients with grand-mal seizures were disappointing. The authors also gave tridione to patients with cerebral palsies and stated that it is of value in reducing tension or rigidity. It was found to be of no particular benefit in chorea, Parkinsonism or dystonia musculorum deformans.

Two fatal cases have been described in patients given anticonvulsant therapy that included tridione. Harrison, Johnson and Ayer<sup>42</sup> reported that a sixteen-year-old girl died from aplastic anemia after having taken tridione and methylphenylethylhydantoin concurrently for six months. Mackay and Gottstein<sup>43</sup> described the case of a twenty-four-year-old man who developed an acute aplastic anemia resulting fatally after taking tridione and phenobarbital for ten months.

Robinson<sup>44</sup> has presented the results of repetition of electroencephalography in adult patients with epilepsy. In 140 patients, of whom 100 had no demonstrable abnormalities and 40 had various types of lesions, the electroencephalogram was repeated after an interval of five to seven years, no essential change in the patients' anticonvulsant therapy having occurred during that time. Among the group without central-nervous-system disease, the electroencephalogram pattern was the same in 85 per cent, worse in 10 per cent and better in 5 per cent. In patients with associated lesions the electroencephalographic tracing was the same in 95 per cent, worse in 2.5 per cent and better in 2.5 per cent. Since the incidence of abnormality could be lowered only in cases in which subsequent electroencephalograms showed improvement, it was evident that the chance of such a decrease was only 5 per cent in the first group and only 2.5 per cent in the second. Thus, a single electroencephalogram taken at any given time has a 95 to 97.5 per cent likelihood

of representing the true electroencephalographic nonconvulsive state of an epileptic adult under unchanging therapy

#### MISCELLANEOUS CONSIDERATIONS

The history of a soldier who for ten years had symptoms of narcolepsy, cataplexy and trance-like catalepsy has been reviewed by Fabing<sup>45</sup>. The condition of the patient was unrecognized, and he went through the Tunisian and Sicilian campaigns of World War II, having repeated attacks during combat. On the basis of analysis of this man, the author elaborates a theory of the pathogenesis of narcolepsy, holding that the fundamental pathophysiologic cause of the disorder is an abnormal susceptibility to inhibition in the brain of the patient.

Two studies have appeared on the rapid production of acute disseminated encephalomyelitis in Rhesus monkeys by the injection of emulsions of brain tissue with dead tubercle bacilli added as an adjuvant. Kabat, Wolf and Bezer<sup>46</sup> produced multiple lesions in such animals in fifteen to thirty days with three injections of emulsions containing either normal rabbit or monkey brain with killed dried tubercle bacilli added as an adjuvant. In previous investigations that did not use adjuvants, thirty to one hundred injections of brain tissue were found to produce similar lesions in three to thirteen months. It was observed that emulsions of fetal rabbit brain (containing no myelin) and emulsions of adult rabbit lung in addition to adjuvants did not induce disease. These investigators believe that the lesions essentially resemble those of acute disseminated encephalomyelitis in human patients. Morgan<sup>47</sup> using similar techniques, arrived at similar results. Particularly interesting are her observations that peripheral-nerve emulsions do not produce these lesions.

Ferraro, Roizin and Hilfand<sup>48</sup> have studied the histologic response of monkey-brain tissue to electric currents similar in type, intensity, duration of flow and frequency to those used in human electric-shock therapy. Pathologic changes were most pronounced in areas of tissue traversed by the main path of the current and, when present, consisted of nerve-cell alterations mostly of the reversible type and distention of perivascular spaces, with perivascular edema, diapedesis of formed blood elements and gutter cells filled with what was presumably hematic pigment. With more intense and longer current flow, occasional petechial hemorrhages resulted. This was considered by the authors to support the thesis that the severity of lesions is proportional to the intensity and duration of the current flow and, to a lesser extent, to the number of shocks given.

Meyer<sup>49</sup> reported that folic acid in daily doses of 15 to 50 mg orally or 20 mg intramuscularly failed to prevent the progression of neurologic symptoms indicative of subacute combined sclerosis in patients with pernicious anemia. With combined liver ex-

tract and folic acid therapy, there was evidence of improvement in signs and symptoms of combined system disease.

Freeman<sup>50</sup> has described 4 cases of amyotonia congenita, or Oppenheimer disease, in which symptoms characteristically appear in infants and consist in paucity of movements, flabby muscles and weak cry. There is a possibility of persistence of life for a number of years, with slight improvement, although most patients with this disease die before the age of eighteen months. Pathologically, Freeman found almost complete absence of large multipolar cells of Betz in the precentral gyrus, together with a great reduction in number of anterior-horn cells at all levels, and a moderate degree of deficiency of multipolar cells in the motor nuclei of the fifth, seventh and tenth but not in the third or eleventh cranial nerves. He suggests the absence of Betz cells as an important point in the pathological differentiation of this disease from infantile spinal muscular atrophy. Freeman also mentions a woman, six of whose children had had amyotonia congenita, who was eventually able to decide whether or not a new baby would have the disease before its birth from the vigor of movements in utero.

The cerebral cortex in the very old human brain has been described by Riese<sup>51</sup>. The brains of 18 inmates of state institutions dying from the ages of seventy-seven to one hundred and seven were studied. A diagnosis of senile dementia had been made in 13 patients, psychosis with cerebral arteriosclerosis in 4 and involutional melancholia in 1. Most of the brains showed some degree of cortical atrophy, diffuse or regional, this feature showing no correlation with the age of the patient or the duration of the disease. The cytoarchitecture was found to be well preserved in all brains. All changes of all types were present, with liquefaction, shrinking and pigmentation most frequent. There was again no correlation with age or duration of illness, and the author was able to establish no connection between the diagnosis and the pathologic findings.

Clarke and Sneddon<sup>52</sup> have reported neurologic findings in a group of 200 internees in Hong-Kong held prisoner from December, 1941, to September, 1945. During that time the internees subsisted on a diet consisting essentially of polished, deteriorating rice, 2 ounces of dried fish daily and occasional additions of beans and green vegetables (usually chrysanthemum leaves). Seventy-four prisoners showed neurologic symptoms, various combinations of optic atrophy, ataxic paraplegia and nerve deafness. At the end of two months of intensive treatment with high-calorie diets, massive vitamin therapy and liver extract, the neurologic symptoms showed no definite improvement.

Thorne and Eder<sup>53</sup> described 5 patients with chronic myopathy associated with thyrotoxicosis. Two of the patients had myasthenia gravis, which

the authors state is only rarely seen accompanying thyrotoxicosis

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## NEW HAMPSHIRE MEDICAL SOCIETY

### PROCEEDINGS OF THE ONE HUNDRED AND FIFTY-SIXTH ANNIVERSARY (Concluded)

House of Delegates, June 18, 19 and 20, 1947

The report of the Committee on Mental Hygiene was then presented as follows

The secretary, Dr Metcalf, has requested that this committee formulate a plan for mental-hygiene clinics, which we prefer to call a survey

Some years ago, through the interest of Dr Dolloff in mental-hygiene work, clinics were established whose purpose was to have persons who had been mentally ill and patients at the state hospital report for follow-up work and assistance in readjusting themselves in the communities to which they had returned. Out of this, clinics soon grew to take care of persons who did not need treatment in the hospital but who needed advice and help because of their emotional difficulties, finally, it became obvious that a full-time director was needed, to establish a series of clinics throughout the state. Dr Anna L. Philbrook, because of her training in psychiatry and in mental-hygiene clinic work and because of her personality, was chosen as director, and this has proved to be a wise appointment.

By her efforts a corps of personnel was formed that at the present time is not capable of fulfilling all the pressure of work put on it and has had to be assisted, through the kindness of Dr Dolloff, by three physicians on the staff of the state hospital: Drs Lombard, Hoyt and Nothmann, Dr Rabin, the director of the psychology department has also given assistance. The work has increased, owing to the facts that so many social agencies are referring cases to the clinics and that, more recently, clinics such as the orthopedic, tuberculosis and pediatric clinics are referring patients for study of personality make-up and emotional status so that they can be trained and rehabilitated to conform better with their type of physical handicaps. It is recommended that the personnel under the director be increased to include a full-time psychiatrist trained in mental-hygiene work, a full-time psychologist and a social worker. These three will prove of invaluable aid in assisting in the work. To acquire this personnel it is obvious that an appropriation of sufficient funds must be made by the state to carry on, and this amount should be \$20,000.

A large percentage of the patients seen have undoubtedly been saved from the development of a psychosis in later years, and from this point of view it can easily be shown that a saving of a considerable amount of money has been made for the state, because the cost of buildings sufficient to care for and treat the mentally ill would, at present, amount to about \$2300 a bed.

Another fact that has been brought out is that a number of children seen in the clinics have been found to have a severe neurosis and to need treatment in a residential setting, where more intensive psychotherapy and treatment could be carried out, and therefore we recommend a home for study and treatment of these children, preferably located on the state-hospital grounds or in close proximity to the grounds so that medical and other facilities of the Hospital can be used to full advantage. At present, the only residential setting for these children in New Hampshire is at the state hospital, where they have to be with adults, which is unfavorable to the children.

Another factor brought out was the rather uneven distribution of the work done in these clinics, which at present cannot be entirely avoided because of the lack of personnel, again showing the necessity for an increase. In Concord, Manchester and Nashua respectively, 124, 68 and 68 clinics were held, whereas in Laconia, Dover, Rochester and Conway respectively, 14, 9, 8 and 1 clinics were held. To be sure, the more thickly populated area of the state is in the southern part, but the north country and the

Connecticut River Valley should receive more attention proportionately than they have been able so far to be given. Owing to the pressure of the larger areas and to lack of personnel, it has been impossible to carry this out as desired.

The total number of visits to these clinics from July 1, 1944, to July 1, 1946, was 4400. One hundred and twelve mental-hygiene talks and classes were given by the clinic director, in addition to these clinics, and 109 staff conferences were held, showing the magnitude of the work that the director has been giving the clinics.

As a result of these clinics one fact that can be evaluated is that the present law limiting the age at which mental defectives can be institutionalized at the Laconia State School should be changed, so that children under five could be sent there if necessary.

Another factor that the committee believed that the State should consider was the employment of the services of a psychiatrist, interested in problems of delinquency, who could assist the courts and probation departments and could also attend to the psychiatric needs of the Industrial School and State Prison.

Another point brought to light was that the percentage of patients suffering from chronic alcoholism is on the increase in the state and that the admission of such patients to the state hospital has definitely increased, the state should begin to treat these patients as mentally ill, for most of them show either neurotic, psychopathic or schizoid traits, and alcohol serves as an escape mechanism. Referring these patients to mental-hygiene clinics could be one of the steps taken to help these patients to rehabilitate themselves without the necessity of committing them to the state hospital, which is already overcrowded.

In conclusion, the committee believes that the value of these clinics and the importance of expanding the Mental Hygiene Clinic system cannot be overstressed, and it is hoped that these recommendations will be referred to the Committee on Legislation for appropriate action.

A. B. HOWARD

Dr Macmillan stated that the Committee on Officers' Reports recommended the adoption of the report of the Committee on Mental Hygiene.

This motion was duly seconded.

The Speaker inquired whether the motion included the question of referral of the recommendations.

Dr Macmillan replied in the affirmative.

Dr Brody referred to several cases of children under five years of age who were mentally deficient and who could not be kept at home, according to the recommendations of the Child Mental Clinic, but who could not be placed. He considered the recommendation for admission to be one of the most valuable things that the Society could do.

Dr Macmillan asked what the age limit was.

Dr Brody answered that it was five years.

The Speaker then requested all those in favor of the motion to signify assent.

There was a chorus of "ayes," and the motion was carried.

The Committee on National Emergency Medical Service was presented by the chairman, Dr Daniel J Sullivan, as follows

It is the considered judgment of the committee that the recruitment of the medical personnel for World War II was performed in a fairly satisfactory manner. The organization and operation of the Procurement and Assignment Service functioned well enough to carry out its mission namely to obtain sufficient medical personnel for the armed forces. It was slow in getting started however. In the event of another national emergency it might be well to have a permanent procurement board consisting of representative members of the American Medical Association and the surgeon generals' staffs already functioning. This general board could then determine age-group quotas for communities and formulate policies for local boards to follow. It is recommended that local boards of doctors be used for procurement and assignment rather than the placing of all the responsibility of procurement on one man in any given community.

In general the medical departments of the armed forces did an excellent job. It is believed that military personnel had sufficient medical care at all times. The quality and character of the medical service to military personnel has been lauded repeatedly. There has been adverse criticism regarding the utilization of medical personnel in the armed forces. In 1941 and early 1942 the flow of doctors into the Army and Navy was not constant nor was it in direct ratio to the size of the rapidly expanding forces. Later in 1942, when the Procurement and Assignment Service reached the peak of its activity, physicians arrived in the service in such large numbers that they were inevitably placed in medical pools awaiting military assignment. In these pools there were sometimes large numbers of doctors with not enough work to keep them busy. It is submitted that if a permanent procurement board were in existence the flow of doctors into the service would be gradual and orderly and based on necessity, as well as more efficient than that in 1941 and 1942. It is believed that the size of the pools would be small, with a consequent saving of countless physician man hours previously lost.

Professional training and supervision of young medical officers should be a constant objective of all senior medical officers. Young medical officers should have the opportunity to do supervised work. In addition some thought should be given to refresher courses for older medical officers. If this is impractical or inexpedient or if it imposes too large an administrative burden more consideration should be given to the utilization of professional skills in making duty assignments. Too frequently physicians with special skills such as roentgenologists were assigned as sole medical officers with isolated units. A refresher course in general medicine or a more appropriate duty assignment would resolve such a situation.

It is believed that civilian medical service during World War II was adequate and effective although it did impose a burden on the physicians remaining in civilian practice. An analysis of a questionnaire on medical care of civilians during World War II by Frank G. Dickinson, Ph.D., revealed that estimations of the increased patient load on civilian physicians during the war averaged 75 per cent. Most civilian physicians, especially in the smaller communities believed that no more physicians could have been spared for military service. Time spent doing examinations for Selective Service boards differed widely among the physicians in any community. It is believed that all qualified physicians in the community should have been required to serve on Selective Service boards.

In the event of another national emergency a reasonable division of the supply of medical services between military personnel and civilians must prevail. In the war about 40 per cent of the practicing physicians were taken into the armed forces leaving 60 per cent of the practicing physicians to take care of 90 per cent of the population that remained civilian. We believe that the next war will be as global in nature as the last was. In the next war however we may expect many casualties and great damage in our own country. During the last war most military physicians believed that there were too many doctors in

military service and most civilian physicians believed that there were too few physicians left at home. These two beliefs are mutually compatible and indicate that the distribution of physicians, in the opinion of physicians themselves, was inequitable. This error must not be repeated in the next war. It is believed that the armed forces could get along with fewer physicians if they made greater use of laymen in administrative positions and employed more technicians for the performance of quasi-medical duties.

A board representing the medical profession and the surgeon generals' staffs empowered to set the policy for the utilization of all physicians could do much to correct the errors that were made in the past and to ensure a more adequate and integrated medical profession for the next great effort. Such a board might well consider the utilization of civilian and military hospitals with their staffs interchangeably for either type of case. The vast scope of atomic warfare might make this necessary.

Dr Macmillan then stated that the Committee on Officers' Reports had approved the report of the Committee on National Emergency Medical Service and recommended its acceptance.

Dr Feiner pointed out that physicians entered the service so fast that they were put into pools, which was not the only reason for misassignments. He believed that there were many cases in which no effort was made to place a man according to his experience and capacities in previous private practice, adding that he had seen breakdowns among men forty-five years of age who served in battalion aid stations and with tank-corps units. Conversely, in a general hospital, there were many young recent graduates with nine months of Army hospital training who were on general service, serving on the surgical service of a fixed institution and who knew nothing about surgery. The burden should have been carried by men with more experience.

The Speaker then asked for a vote on the motion to accept the report.

The motion was carried.

Dr D. G. Smith expressed approval of the report of the Committee on National Emergency Service, adding that the House of Delegates of the American Medical Association at its recent meeting had voted to approve the following recommendation: that the Congress and the President of the United States be respectfully urged to provide that the surgeons general of the Army, Navy and Air Force be made members of the Joint Chiefs of the General Staff, to require that the Secretary of the Navy and the Secretary of War, or other cabinet officers charged with the responsibility for national defense in the planning, location and construction of military hospitals in their wartime utilization, give consideration to possible civilian wartime requirements, and that they re-examine their organizational tables and other procedures used during World War II, to avoid a repetition of medical overstaffing of units, the wasting of the time of doctors of medicine in the performance of unprofessional duties, which could have been performed effectively by nonmedical personnel, removal of the excessive number of doctors of medicine from civilian hospitals and civilian prac-

tice and an effort to avoid the rather widespread failure to make assignments, determine rank and provide for the rotation of doctors of medicine on the basis of their professional qualifications, experience and age. It was also recommended that a National Emergency Medical Service Administration be created as a continuing function of government, considering the representatives of American physicians and surgeons, in such organizations as the American Dental Association, American Medical Association, American Nurses' Association, American Veterinarian Medical Association and Association of American Medical Colleges. The next recommendation was that the responsibility at all times for effective plans for total mobilization of the medical and allied resources of the nation was the duty of the national administration. The final recommendation was that the Committee on National Emergency Medical Service be continued until such time as the purposes for which it was created have been fulfilled. It was voted that the states be asked to continue their committees on national emergency medical service.

The next report was that of the Committee on Tuberculosis.

The year 1946 recorded a definite increase in the mortality from all forms of tuberculosis in New Hampshire as compared with the all-time low of 1945. The Division of Vital Statistics of the New Hampshire Department of Health reports a total of 115 deaths and a death rate of 24.8 per 100,000, as compared with 96 deaths and a rate of 21.9 in the preceding year.

The statistics for the other states and the nation as a whole are not available at present. Therefore, it is not possible to present a comparative study of the position of New Hampshire among the states as it relates to tuberculosis mortality in 1946.

In 1945, however, New Hampshire occupied an enviable position among the states in this respect. It had the lowest tuberculosis death rate in New England, 21.9 per 100,000 population as compared with a rate of 31 in Maine, 33.2 in Rhode Island, 35.4 in Vermont, 37.2 in Connecticut and 39.3 in Massachusetts. Among the states New Hampshire was in the seventh place among the states with low rates: Wyoming, 10.9; Utah, 12.8; Nebraska, 15.4; Iowa, 15.7; Idaho, 16.2; Kansas, 19.5; and New Hampshire, 21.9. New Hampshire's position is particularly noteworthy in view of the fact that it stands third among the states from the standpoint of population to industrial employment, Rhode Island standing first and Massachusetts second.

The increase in tuberculosis mortality for New Hampshire for 1946 is approximately 20 per cent — or 4 points in rate — as compared with the previous year. Several important criteria must be considered in evaluating the 1946 tuberculosis mortality. The trend in the death rate from an infectious disease is based on the evidence of increase or decline over a three-year or five-year period. On that basis, the tuberculosis death rate has persistently declined in New Hampshire over the past thirty years from 1916 to 1920 the annual average rate was 114 per 100,000, from 1921 to 1925, 76.8, from 1926 to 1930, 59.7, from 1930 to 1935, 30.6, and from 1941 to 1945, 25.2. Furthermore, some fluctuation is to be expected in the tuberculosis death rate from year to year, especially in that for a state with a small population.

The apparent increase in New Hampshire in 1946 follows a sharp decrease of approximately the same magnitude in 1945. The reported rate for the three-year period 1939 to 1941 was 27, and that for the three-year period 1942 to 1944 24.5. The rate then dropped to 21.9 in 1945, and

in 1946 returned to approximately its earlier level. The corresponding number of deaths was an annual average of 135 for the years 1939 to 1941, 117 for 1941 to 1944, 96 for 1945 and 115 for 1946. In relation to the figures for other years the death rate for 1945 is seemingly aberrant, and little or no significance can be attached to the apparent increase in the rate for 1946.

Under the continued leadership of the medical profession and the organized public-health and voluntary agencies, the program for the eradication of human tuberculosis is marching on to increasing success. We are fully cognizant of the fact that more effort and aggressive campaigning are required to maintain and reduce still further a low tuberculosis death rate than a high one.

The committee wishes to re-emphasize that the most important of all case-finding agencies in the state of New Hampshire in the fight against tuberculosis continue to be the practicing physicians. It is almost always true that the family physician has the first opportunity not only to ascertain the presence of active pulmonary tuberculosis but also to give battle for the cure of the afflicted and the safeguarding of the other members of the family from the tubercle bacillus, for it is the family physician to whom most people go when troubled by signs of ill health.

The records in the chest diagnostic clinics prove that the physicians of the state, if they are determined to do so, can perform a better job of suspecting and discovering active tuberculosis cases, year in and year out, than any other agency. It is noteworthy that in the past year, as in other years, more cases of active pulmonary tuberculosis were found among the referrals by physicians to the chest diagnostic clinics than in any other groups of people examined.

The Committee wishes again to urge increasing use of chest x-ray examination. It is now clearly demonstrated that tuberculosis can be seen on the chest x-ray film before it can be heard by use of the stethoscope. This is particularly true in the discovery of early or minimal cases.

Over 4300 chest x-ray films were taken in the case-finding programs in the chest diagnostic clinics, schools and colleges in 1946, in addition to the large numbers taken in the hospitals throughout the state.

We urge continued use of the tuberculin test, particularly among young people, and efforts for the discovery of possible "spreaders" among the adult contacts of children presenting positive reactions to the test.

Efforts for the promotion of routine chest x-ray examination for all patients admitted to general hospitals have been handicapped because of lack of personnel and the rationing of x-ray films. It is hoped that an evaluation of this case-finding procedure can be made in one or two hospitals in the near future.

During the past year there has been a considerable amount of publicity in the newspapers and magazines about a newly discovered "cure" for tuberculosis — streptomycin. According to reports from the United States Public Health Service and the National Tuberculosis Association this publicity has given an unjustifiably optimistic picture. Despite considerable research activity it is stated by these sources that the full value of streptomycin treatment is not yet known and that the indiscriminate use of the drug is not advocated by medical opinion. According to present indications, streptomycin in the treatment of pulmonary tuberculosis appears to have its greatest usefulness if given in the early stages of the disease, in the later stages, when there has been extensive destruction of lung tissue, the drug has shown little to encourage a belief in its effectiveness. In some minimal cases, good results have been reported, but most patients with minimal cases recover on older methods of treatment without the use of streptomycin.

To advocate the indiscriminate use of streptomycin, especially in moderately advanced or advanced cases of pulmonary tuberculosis, not only is premature but also carries with it certain dangers and drawbacks. Among the principal dangers in the use of this drug is its toxicity, which may seriously affect hearing, sight and kidney function and cause skin eruptions. At present, it can only be said that we have seen little in the treatment of well-established pulmonary tuberculosis by streptomycin that gives cause for any great optimism regarding its curative value.

The use of streptomycin, however, has stimulated the development of research activities by national health agencies and other groups. There remains the possibility, not yet explored, that streptomycin or some related mold offers a chance for the discovery of a curative measure of value. It is believed that years of careful research will be required to bring forth the facts concerning the value of streptomycin.

During the past year considerable attention has been directed to the possible use of BCG (*Bacillus-Calmette-Guérin*) in this country as an immunizing agent against tuberculosis. In 1908 Calmette and Guérin announced in Paris the development of a particular strain of bovine tubercle bacillus that had lost its virulence twelve years later they reported that this culture was harmless to man and was effective in bringing about some measure of immunization against tuberculosis. Several million vaccinations have been performed since the initial work with human beings in 1921. Although extensive vaccinations have been carried out in Europe and South America, and careful studies undertaken in the United States BCG vaccinations have not been well accepted in this country.

Last September a conference on BCG vaccination was held in the offices of the Tuberculosis Control Division of the United States Public Health Service. The consultants constituted an assemblage of tuberculosis authorities in the United States and from Denmark and China.

Briefly, a few of the conclusions were that BCG should not be made commercially available at present, that a single laboratory be established by the Tuberculosis Control Division of the United States Public Health Service to produce BCG vaccine for the whole country for use in research programs proposed at the conference, that extensive investigations be carried on co-operatively with recognized research groups throughout the country during the coming years, especially in population groups highly exposed to tuberculous infection and that the United States Public Health Service set up a controlled study in a community containing 100,000 or more people, to determine immediate and long range results.

Although discoveries have been and are steadily being made it is well to remember the advice. Be not the first by whom the new is tried, nor yet the last to lay the old aside. Research and experiment will determine the value of the new drugs and treatments, but it is poor judgment to discard anything good unless for something really better. The value of BCG is still the subject of argument, and streptomycin is not a demonstrated aid in cure and has serious disadvantages. In New Hampshire experimental methods seem to be out of place while the well demonstrated fundamental procedures in the discovery, diagnosis, prevention and treatment of tuberculosis continue to win results. We must continue and extend these well developed resources, ever hopeful that a cure or preventive for human tuberculosis will be found and thus hasten the victorious conclusion of our struggle.

One of the members of our Committee Dr. Richard C. Batt, has left New Hampshire hence this report is prepared by the other two members.

ROBERT B. KERR, Chairman  
JOHN D. SPRING

Dr. Macmillan, for the Committee on Officers' Reports, recommended adoption of this report.

This motion was duly seconded and was carried.

Dr. Perreault, in presenting the report of the Committee on Communications and Memorials, read the following communication to Dr. Metcalf from Dr. Norman H. Gardner, of the Committee on Rural Medicine of the American Medical Association.

I am writing to again urge you to form a state Committee on Rural Medical Service to co-operate with the national committee. It is now more than ever essential that organized medicine present a common front of interest in the welfare of the rural dweller. I need not remind you that organized medicine has been attacked by many in the immediate past. The farmer has given all in-

dications of being anxious and willing to work with us to formulate plans for improvement in the medical situation of those living in rural areas.

There is much of a constructive nature that a Committee on Rural Medical Service can accomplish. In your state as in my own I presume that the problem is largely one of educating the farmer as to just what constitutes good medical care, and by what means he may attain the goal.

We in Connecticut are now in the process of planning our first Conference on Rural Health. The steering committee is most enthusiastic, and it looks as though we will have a very interesting conference.

Medicine has definitely taken the lead in this matter of rural health and we should continue to carry the ball now that we have it. There are not a few on the radical fringe who are most willing and anxious to step in and finish the job in their own way. We must not let this happen.

I sincerely hope that I will hear in the near future that your state has formed a committee on Rural Medical Service. I shall plan to meet with the chairman to talk over plans for the work of the committee in New Hampshire.

Dr. Perreault stated that the Committee recommended that a committee for rural medical service be appointed to co-operate with the national committee.

This motion was duly seconded.

Dr. Dye inquired whether the new group was to be a standing or a special committee.

Dr. Perreault replied that the Committee believed that it should be as standing as the national committee.

The Speaker then asked for a vote on the motion.

The motion was carried.

Dr. Perreault then read the following letter from Miss Helen E. Hinman, nutrition consultant of the State Department of Health, addressed to Dr. Sycamore.

Upon a request from Dr. Colin Stewart, I am writing you the reasons why I think a nutrition committee of the State Medical Society would help promote better nutrition in New Hampshire.

Through such a committee, advice and co-operation could be given on the publication of nutritional material by the State Health Department. Because of the recognition of the importance of nutrition in geriatrics, pediatrics, pregnancy and surgical cases as well as other diseases where nutrition is considered an important part of the treatment, it would be helpful if such a committee could give information on the latest nutritional research to the county organizations and suggests names of speakers to them in these fields.

It has been stated in the *American Medical Journal* that nutrition has been found to be important to a patient in the recovery of various surgical diseases. Therefore it is necessary for the physician to know the kind of foods the patient needs. It is no longer enough to give orders as "give the patient light, soft, solid diet." He must now know the amounts of protein, vitamins and so forth the patient requires. And the now recognized routine in post-operative cases of intravenous alimentation with protein digest, plasma, and vitamins makes it a more complicated nutrition problem than it was formerly. Therefore, information of the latest research in this field becomes of aid to the physician.

In pediatrics the mass of information on nutrition obtained through the study of animals has been supplemented and augmented by the study of well and sick children. So that now nutrition in pediatrics includes much more than giving required amounts of appropriate foods in health. It requires an understanding of metabolic changes in diseases and the compensating for these changes.



In the whole field of nutrition nothing has been more dramatic than the studies done on nutritional requirements during pregnancy and the application of this knowledge is not only important for the patient but also for future generations. And yet, in many communities in New Hampshire, I find expectant mothers not getting necessary foods and physicians tell me that in some communities that they do not have more than two or three breast-fed babies in the town. Last month I visited a maternity home where the manager told me that they had not more than one breast-fed baby a year in that home. And yet, a recent report of Aldrich at Rochester gives seventy-five per cent breast feeding in their clinic. I think the physicians could do much to encourage breast feeding in their communities. We find pre-school feeding hardly ever a problem if infant feeding is right.

My work as nutrition consultant for the New Hampshire State Department of Health is to promote better nutrition for all age groups. I think a nutrition committee would be of great service to me in informing the physicians of the nutritional problems in their community and their advice and co-operation would help me in my work.

Dr Perreault then stated that the Committee did not consider the establishment of a new committee on nutrition to be quite essential, since there was already a committee on child health, maternity and infancy.

Dr Feiner expressed agreement, pointing out that the proposal presupposed that the majority of surgeons did not know about parenteral feedings, protein requirements and fluid balance and that the obstetricians did not know how to feed pregnant women, it threw the blame for bottle and formula feeding squarely on the shoulders of the doctors, when it is really the fault of the mothers, who insist on it. He did not believe that there would be much gained by instituting another committee involving additional expense.

A member moved that the recommendation of the committee be accepted.

This motion was duly seconded and was carried.

Dr Perreault then read the following communication from Dr Frederick J Vintinner, director of the Division of Industrial Hygiene, addressed to Dr John Samuel Wheeler, state health officer.

As part of the industrial health and hygiene program in New Hampshire it is believed that an active committee on Industrial Health, in the New Hampshire State Medical Society would aid materially in the advancement of this program among industrial officials and employees. While it is understood that the present Health Committee of the Society assumes these functions in addition to other problems relating to public health, a Committee on Industrial Health with members who are actively engaged in industrial medicine would be of considerable assistance in the development of standards, practices and procedures necessary for the development of good industrial health programs.

Committee membership of such physicians as Dr Robert Graves, Concord, Dr David Parker, Manchester, Dr Henry Almond, Berlin, Dr Robert W Holmes, Keene, and Dr Timothy F Rock, Nashua, would give representation of physicians actually engaged in industrial medicine.

Such a committee would be of great value to the Division of Industrial Hygiene, State Health Department, in the development and advancement of the industrial hygiene program in New Hampshire.

Dr Perreault stated that the Committee believed that a committee on industrial health should be appointed, unless there are other committees at the present time that could do this. He made a motion to that effect.

This motion was duly seconded and was carried.

Dr Perreault then asked for discussion concerning Senate Bill No 86, dealing with the sale of barbiturates. The bill was as follows:

*Be it Enacted by the Senate and House of Representatives in General Court convened*

I DEFINITIONS For the purpose of this act,

I The term "barbiturate" means the salts and derivatives of barbituric acid, also known as Malonyl Urea having an hypnotic or somnifacient action, or compounds of any preparations or mixtures thereof.

II The term "delivery" means sale, dispensing, giving away, or supplying in any other manner.

III The term "patient" means, as the case may be, (1) the individual for whom a barbiturate is prepared or administered, (2) the owner or agent of the owner of the animal to which a barbiturate is administered or for which a barbiturate is prescribed.

IV The term "person" includes individual, corporation, partnership and association.

V The term "practitioner" means a person licensed by law to prescribe and administer barbiturates.

VI The term "pharmacist" means a person duly registered with the state commission of pharmacy as a compounder, dispenser, and supplier of drugs upon prescription.

VII The term "prescription" means a written order by a practitioner to a pharmacist for a barbiturate for a particular patient, which (1) specifies the date of issue, the name and address of the practitioner, (2) the name and address of the patient (and if such barbiturate is prescribed for an animal, the species of the animal), (3) the name and quantity of the barbiturate prescribed, (4) the directions for use of such drug, and (5) the signature of such practitioner.

VIII The term "manufacturer" means persons other than pharmacists who manufacture barbiturates, and including persons who prepare such drugs in dosage forms by mixing, compounding, encapsulating, entablating or other process.

IX The term "wholesaler" means persons engaged in the business of distributing barbiturates to persons included in any of the classes named in section 3, paragraph c.

X The term "warehousemen" means persons who store barbiturates for others and who have no control over the disposition of such barbiturates except for the purpose of such storage.

2 PROHIBITED ACTS No person shall I Deliver any barbiturate, except as provided in paragraph III of section 3 unless Such barbiturate is delivered by a pharmacist, upon an original prescription, and therefore is affixed to the immediate container in which such drug is delivered a label bearing the name and address of the owner of the establishment from which such drug was delivered, the date on which the prescription for such drug was filled, the number of such prescription as filed in the prescription files of the pharmacist who filled such prescription, the name of the practitioner who prescribed such drugs, the name and address of the patient, and if such drug was prescribed for an animal, the statement showing the species of the animal, and the directions for the use of the drug as contained in the prescription, or II Refill any prescription for a barbiturate unless and as designated on the prescription by the practitioner, or III Deliver any prescription for a barbiturate unless the pharmacist who filled such prescription files and retains it as hereinafter required, or IV

Possess a barbiturate unless such person obtained such prescription by a practitioner or V. Refuse to make available and to accord full opportunity to check any record or file, as required herein VI. Fail to keep records as required herein or VII. Use to his own advantage, or reveal (other than to an officer or employee of the state department of pharmacy or to a court when relevant in a judicial proceeding) any information required under the authority of section 4 concerning methods or processes which as a trade secret are entitled to protection.

3. **EXEMPTIONS.** I. Nothing in this act shall apply unless otherwise indicated by the practitioner to the refilling, at any time of a prescription for compounds, mixtures or preparations containing in addition to a barbiturate, sufficient quantity of another drug or drugs to cause the compound, mixtures or preparations to possess other than an hypnotic or somnifacient action.

II. Nothing in this act shall apply to any compound or mixture or preparation that is intended to be used as a spray or gargle or a liniment or in any other way for the external application if such compound, mixture or preparation contains in addition to the barbiturate, some other drug or drugs rendering it unfit for internal use and such compounds or mixtures or preparations shall be sold in good faith for the purpose for which they are intended and not for the purpose of evading this act.

III. The provisions of section 2, paragraph IV shall not be applicable (a) to the delivery of barbiturates to persons included in any of the classes hereinafter named or to the agents or employees of such persons for the use in the usual course of their business or practice or in the performance of their official duties as the case may be or (b) to the possession of barbiturates by such persons or their agents or employees for such use.

(1) pharmacists (2) practitioners (3) persons who procure barbiturates (a) for disposition by or under the supervision of pharmacists and practitioners employed by them or (b) for the purpose of lawful research teaching, or testing and not for resale. (4) hospitals and other institutions which procure barbiturates for lawful administration by practitioners. (5) officers or employees of federal, state or local governments or (6) manufacturers, wholesalers, carriers, warehousemen.

4. **RECORDS.** I. Persons, other than carriers and practitioners shall keep complete records showing (1) all stocks of barbiturates on hand and (2) all receipts and deliveries of barbiturates by such persons their agents or employees.

II. Practitioners shall keep complete records showing (1) all stocks of barbiturates on hand July 1st, 1947, (2) all receipts of barbiturate by them, their agents and employees and (3) the name and quantity of each barbiturate dispensed or administered by them (4) the date it was dispensed or administered by them (5) the name and address of the patient, and (6) if such barbiturate was prescribed for or administered to an animal the species of the animal.

III. Pharmacists shall keep complete records showing (1) all stocks of barbiturates on hand July 1st, 1947 (2) all receipts of barbiturates by them (3) file each prescription received by them with appropriate number and date of each refill pursuant thereto, (4) retain such prescriptions for a period not less than two calendar years immediately following the date of the last filling or refilling (5) in the case of sales under the provisions of section 3 paragraph III, the names and quantity sold the date it was sold and the name and address of the purchaser.

IV. The usual commercial or other records maintained by manufacturers, wholesalers, practitioners or pharmacists with the exception of the inventory of the initial stock on hand shall suffice to meet the requirements of this section. Such records shall be preserved.

V. Persons required by this section to keep files or records relating to barbiturates shall upon the written request of an officer or employee duly designated by the state department of pharmacy (1) make such files or records available to such officers or employees at all

times for inspection and copying and (2) accord to such officers or employees full opportunity to check the correctness of such files or records including opportunity to make inventory of all stock of barbiturates on hand and it shall be unlawful for any such person to fail to make such files or records available or to accord such opportunity to check their correctness.

5. **REGULATIONS.** The state department of pharmacy is hereby authorized to promulgate necessary regulations for the administration and enforcement of this act.

6. **PENALTIES.** Any person who violates any of the provisions of this act shall be fined not more than one thousand dollars nor less than five hundred dollars.

7. **TAKES EFFECT.** This act shall take effect July 1 1947.

The following letter from the legislative committee of the New Hampshire Pharmaceutical Association was then read

June 3 1947

Dear Doctor

Medical practitioners and pharmacists have been subjected to unfortunate criticism by the general public by spokesmen for women's clubs, by the writers for pulp magazines and by the press in connection with the increasing amount of Barbiturates distributed per capita. This pressure has caused Congresswoman Edith Nourse Rogers (Mass.) to introduce the present Barbiturate Bill now before Congress. This Bill will provide for the safe keeping of records, inventories and inspections as for Narcotics.

To correct public opinion that Barbiturates are distributed indiscriminately by medical practitioners and pharmacists, and to avoid the onerous Federal regulations of pending legislation this state society has introduced on the state level the enclosed bill. Restrictions on both practitioners and pharmacists are at the minimum. Records are reduced to invoices of goods received and the usual medication entries made on the patient's case record in the doctor's office. (Duplicate printed original inventory forms will be mailed you from this office subsequent annual inventories are not required.)

There are no restrictions on the amount or frequency of administration or dispensing by the practitioner. No pharmacist may refill without specific directions.

The above facts should serve to correct completely the erroneous reports concerning the Bill circulated before it was even printed.

A reading of the Bill will demonstrate that its object is protection for the public, prevention of undesired criticism of practitioners and pharmacists, and the reduction of restrictions to a minimum of state control rather than by Federal legislation.

The American Medical Association supports even the more restrictive Federal form of this same legislation. Dr. Austin Smith, Chairman of the Committee on Pharmacy and Chemistry, helped draft the legislation.

We look forward to your professional support of "Senate Bill No. 86."

Respectfully

HENRY J. ROBERTS  
Chairman, Legislative Committee

Dr. Sullivan believed that the bill had originated with the Pharmaceutical Association, who apparently thought that regulation was needed. Incidentally, in regulating themselves, the Association proposed to regulate the medical profession. He stated that if the Pharmaceutical Association considered regulation regarding the dispensing of barbiturates to be necessary, the New Hampshire Medical Society should not be taken into the provisions of the bill, which would entail a great deal of work. Certainly, the Federal Narcotic Bureau did not demand such

strict accounting of narcotics as this bill demanded of barbiturates. He believed that these restrictions should be struck out entirely, and the provisions of the bill confined to regulating pharmacists.

Secretary Metcalf stated that at a recent hearing Drs Tuttle and Howard Sawyer had spoken, as well as the President of the Veterinary Association and Dr Metcalf.

About eight weeks previously, Henry Roberts, chairman of the Legislative Committee of the New Hampshire Pharmaceutical Association, had asked the New Hampshire Medical Society to support the bill. Dr Metcalf had heard nothing further from any member of the Pharmaceutical Association until after the bill had been submitted to the Senate. On the other hand, the Pharmaceutical Association sent out to each pharmacist a letter in which it was stated that the Secretary of the New Hampshire Medical Society had stated that he saw no objection to the tentative bill. Dr Metcalf pointed out to the Senate Committee that that was technically true — that he had not stated objection to the bill, nor had he stated that he favored it.

In the few remaining days Dr Metcalf communicated with about ten physicians in the state: two in Nashua, two in Manchester, two in Dover, two in Wolfeboro and two in Hanover and several in Concord, all of whom objected to the bill as it is now written because the barbiturates are now controlled by regulations of the New Hampshire Board of Health and this was apparently an effort on the part of the Pharmaceutical Association to take the authority away from the Board of Health and transfer it to the Department of Pharmacy — a sort of jurisdictional quarrel.

One objection was the paper work involved in keeping this list of barbiturates and the name of the patient and the reason for which it was given, the amount that was given and so forth. When that objection was raised, Dr Metcalf was told that it would not be necessary to keep a special list but that the regular office records of the patient would suffice, to which he replied that the regular office records contained other data, such as the history of the patient, the diagnosis and the clinical findings, and that those should not be open to inspection, because the Pharmaceutical Association proposed under this bill to send an inspector to the doctor's office to examine the records.

The next objection was that the penalties were too high. The minimum fine was \$500, and the maximum \$1000, which perhaps would not be too high for a physician, if there is one in the state who is giving these drugs to addicts, but it was certainly too high for any honest doctor who simply had a record that was not complete.

Then, Dr Metcalf had told the Senate and Mr Roberts had also told the Senate that this particular bill, as written, should be tabled, that if there was any need for legislation, the pharmacists should get

together with the doctors and the Board of Health and work out any legislation that was needed, the pharmacists, as a matter of fact, had written the bill without consulting either the Board of Health or any doctors.

Dr D G Smith then observed that the statement that the American Medical Association had supported even the more restrictive federal forms of this same legislation was absolutely untrue, of which he had proof in the minutes of the meetings.

Apparently, in some states, there was necessity for the regulations. In 1945 fourteen states and the District of Columbia had no restrictions on these barbiturates, so that they could be sold over the counter. One of the states was Massachusetts. In some states, where the laws had been passed prohibiting the sale of the barbiturates over-the-counter, it was not enforced. There had been an effort to draft a uniform barbiturate bill, and it stated in the hearing that such a bill has been presented in some of the states. One of the senators from New Hampshire said that the testimony at the hearing was that this bill was introduced in the New Hampshire Senate as the uniform bill.

Mr Holloway, director of the Bureau of Legal Medicine, stated that the New Hampshire bill was not the uniform bill, that the bill as introduced in the various states had some defects and that in July or early August, he was going to meet with the counsel of the American Pharmaceutical Association and another group to draft uniform state regulations in an attempt to draw up a uniform barbiturate bill that would be acceptable. When he was told that physicians in New Hampshire were trying to kill the present bill, he replied that he thought they were justified in doing so.

Of three senators on the Public Health Committee of the Senate, one had definitely stated that he would go along with the doctors, one was favorable toward physicians, and the third appeared to be on the fence. Dr Smith had been informed, however, that the bill would not be reported out of committee, which would shortly meet again.

Dr Dube moved that the House of Delegates go on record as opposing Senate Bill 86.

This motion was duly seconded and was carried. Dr Dye asked if someone were going to be delegated to inform the Senate Committee about the Society's stand.

The Speaker replied that the President of the Society would take such steps.

Dr Perreault then referred to a communication from Dr Oppenheimer, asking if the Society could organize or become connected with a good medical library from which members could borrow books and periodicals without red tape, high cost and waste of time. It was the opinion of the Committee on Communications that that would not be necessary, for most large cities had their own libraries and medical libraries were available.

Dr Brody inquired what was meant by the statement that medical libraries were available.

Dr Perreault replied that at Harvard Medical School one could find all the material desired and that, through the American Medical Association, necessary information could be obtained. The American College of Surgeons also had a library, where one could look up information. At Rochester, a recent but fairly active library was available to all the members of the New Hampshire Medical Society.

The Speaker pointed out that no action was required on this matter.

The Delegate to the American Medical Association, Dr Deering G. Smith, then presented the following report:

Three sessions of the House of Delegates of the American Medical Association have been held since the last meeting of the Society, and to make this report brief only the high spots will be brought to your attention. Your delegate served on the following important reference committees at each session—Legislation and Public Relations Executive Session and Reports of Officers.

At the San Francisco session President Roger Lee urged a wider participation of physicians in public and world affairs. Since the younger members of the medical profession will be most concerned with the changing order of medical practice, they should have a large share in the affairs of county and state societies and in the American Medical Association. Dr Olin West resigned after being secretary for twenty-four years. Dr West was chosen president-elect, but this spring he had to resign because of ill health. He was succeeded by the vice-president, Dr Edward L. Bortz, who is now president. Dr George F. Lull retired from the Army after serving as deputy surgeon general, was selected as secretary and is filling the position in an admirable manner.

In view of the agitation for a second medical school in this state, it seems advisable to summarize the requirements for a new medical school as was brought out in a committee report: Initial expenditure of millions and annual budget of \$350,000 for the school alone, full time clinical instructors, ample supply of ward patients and competent instructors, including specialists. The annual number of graduates from the existing schools is adequate for the peacetime needs of the country; granted distribution is equitable. In New Hampshire the physician population has increased more than the general population and even the rural areas have adequate medical care.

A resolution was unanimously adopted that "proposed legislation such as that of S. 1606 (relating to compulsory health insurance), if ever enacted would seriously jeopardize the proper and adequate care of sick people in the United States."

To improve the public relations of the Association it was voted to stress the scientific activities through the *Journal* and through an expanded *Hygiene* to expand the Bureau of Medical Economics with the employment of competent economists and to appoint an executive assistant to the general manager to co-ordinate all public relations activities other than scientific. At the supplemental session held at Chicago in December this was amplified to include the description and dramatization of the progress of scientific medicine and the history of organized medicine in the United States, as well as increased activity in health education by means of the radio and motion pictures.

At this supplemental session there was some discussion of the general practitioner and the Section on General Practice was requested to give consideration to a plan for the establishment of a certifying board. The following resolution was voted:

Hospitals should be encouraged to establish general practice services. Appointment to a general practice section shall be made by the hospital authorities on the

merits and training of the physician. Such a general practice section shall not per se prevent approval of a hospital for the training of interns and for residencies. The criterion of whether a physician may be a member of a hospital staff should not be dependent on certification by the various specialty boards or membership in special societies.

This statement was repeated and amplified at the recent session at Atlantic City. It was most fitting that the discussions in the House of Delegates at this centennial session should center on the general practitioner or family doctor. This was also true at the Conference of County Medical Society Officers held this year for the first time. It was agreed that a place must be found in the hospitals for the general practitioner who does the major portion of the medical work, and that there must be no discrimination against him and no priority given to specialists in admitting patients to the hospitals. Every patient should have the free choice of his physician, even in a hospital. There is an insufficient number of hospital beds, owing partly to the demands of members of hospitalization plans and county societies should stimulate additions to hospitals. It was suggested that medical films, of which the American Medical Association has many, as well as lists of all others, be used to increase attendance at county meetings and that the rural general practitioners be urged to read papers. In some societies lectures are given to all new members, stressing the history and structure of organized medicine, public relations and the prevention of malpractice suits. In other societies there is a probationary period of six to twelve months, during which the applicant has all privileges except voting before he becomes a full member. It was voted to have another conference next year, and it was suggested that each state organize a county secretary society. This state had meetings of the county secretaries years ago that were well attended and of great value.

The Atlantic City session—the one hundredth anniversary—was attended by over 15,000 physicians the largest attendance by many thousands, in the history of the American Medical Association. Foreign guests leaders in their countries, were present and read papers. Distinguished nonmedical persons gave addresses. A stamp commemorating "The Doctor" was issued, and President Truman sent a cordial message. President Shoups stated "that the immediate and most urgent needs are concerned with increasing the availability of the services of General Practitioners." There is too much specialization and the reinvigoration of general practice is necessary. Following his recommendations it was voted to request the Board of Trustees to appoint a special committee including a number of general practitioners to study and report on all the factors that affect the production and distribution of the type and quality of medical care that the people need or desire.

A year ago the supplemental session of the House of Delegates was instituted and this year it was decided that this annual session would be held in various sections of the country to be preceded or followed by a scientific session devoted exclusively to the general practitioner.

It was recommended that, to obtain a greater number of well qualified speakers the Council on Medical Service assist in the establishing of a speakers training program and speakers bureau in every county medical society, bring its pamphlets up to date and prepare a number of basic speeches for distribution through the speakers' bureaus.

Many county and state societies have overlooked the potent public relations value of their women's auxiliaries and it was voted to urge the societies to have their auxiliaries make use of available material at the headquarters office.

The nursing crisis was discussed and the president was asked to appoint a committee to investigate the present objectives of the nursing profession, the standards of education, the time involved for training, the various curricula, the supply of nurses and quality of services rendered, remuneration participation in the determination of administrative policies, the question of security benefits and the study of the training of practical nurses.

Thirty-eight states have worked out plans for home-town medical care of the veteran but the Veterans Administration

approve Dr Ford's acceptance of an appointment to this committee.

The Secretary pointed out this was a committee of ophthalmologists, who met at specified intervals with the Department of Public Welfare, to consider the care of the blind, and to advise on proper measures to be taken by the Department of Public Welfare. This was a formality to add Dr Ford to this Consulting Committee.

Dr Macmillan moved that Dr Ford be added to the Medical Advisory Committee of Ophthalmologists.

This motion was duly seconded and was carried.

The Speaker stated that at the meeting on the previous evening, every delegate was present except one, who sent a letter of explanation to say that he could not come and for whom there had been an alternate. At the morning session, all were present except two.

Dr Parsons then proposed the following names for life membership: Drs E. R. Dell, of Berlin, R. E. Webb, of Lancaster, and John M. Blodgett, of West Stewartstown. Dr Feiner moved that the names be accepted.

This motion was duly seconded and was carried.

Dr Dye then presented the proposed amendment to the by-laws, as brought forth the previous night and laid on the table for one day. It was more or less a matter of routine to change Chapter VIII, Section 1, of the by-laws, under the heading of Committees, and add, "A Committee on Industrial Health" and also to add "A Committee on Rural Medical Service." These additional committees would occupy an additional section at the end of Chapter VIII. He moved that these changes in the by-laws be accepted.

This motion was duly seconded and was carried.

Dr Macmillan stated that the Committee on Officers' Reports wasted a great deal of time in reading in detail some of the long reports, and he wondered if the committee could bring in a summary of those reports and bring out the salient features, that would give an opportunity for more time for discussions.

Dr Dunbar recalled having experienced the same difficulty when he had been chairman of the committee. He believed that if some changes could be made, it would save a good deal of time.

The Speaker asked if it would be feasible to mimeograph reports and send them to the delegates.

The Secretary replied that such a procedure had been tried one year, the reports had been late in coming in, the synopses had been fragmentary, and the change had seemed not to be worth while. He stated that if the Chairman of the Committee on Officers' Reports could make brief abstracts of the various reports, he would be glad to have them printed or mimeographed and sent to each delegate in advance, it would give the delegates some idea of what was coming up.

The Speaker asked if it would be possible to mimeograph the full reports, if they came in on time, and then have the Chairman of the Committee on Officers' Reports present the synopsis at the meeting for discussion.

The Secretary answered that that would be possible. It would involve a good deal of work and expense, but he would be glad to do anything the House of Delegates directed, to get the information out.

Dr Macmillan moved that it be the duty of the Committee on Officers' Reports to submit at the time of the meeting of the House of Delegates a summary of each committee's report, to be read in place of the full report, except in cases in which the report was requested to be read in detail.

Dr Lewin stated that during the previous year he had received two of the reports after he arrived at the medical meeting, which was held about two hours before the delegates' meeting.

Dr Dunbar stated that it appeared to him that the Secretary knew the technical difficulties of the situation and that the matter should be left to the Secretary's discretion.

The Speaker called for a vote on the motion.

On a showing of hands, 12 were for the motion, and 6 dissented, therefore, the motion was carried.

The second meeting of the House of Delegates was adjourned at 9:45 a.m.

\* \* \*

The House of Delegates reconvened at the Wentworth Hotel, Newcastle, on June 20, 1947, at 9:00 a.m. with Speaker Sycamore, of Hanover, presiding.

The following members answered the roll call:

The President, *ex-officio*  
 The Vice-President, *ex-officio*  
 The Secretary-Treasurer, *ex-officio*  
 Samuel Feiner, Ashland  
 Nathan Brody, Laconia  
 W. J. Paul Dye, Wolfeboro  
 Francis J. C. Dube, Center Ossipee  
 Marjorie A. Parsons, Colebrook  
 Joseph E. Laroche (alternate for Francis M. Appleton)  
 Israel A. Dinerman, Danaan  
 Leslie K. Sycamore, Hanover  
 Clarence E. Dunbar, Manchester  
 Daniel J. Sullivan, Nashua  
 Samuel Fraser, New Boston  
 Loren F. Richards, Nashua  
 Robert R. Rix, Manchester  
 Philip M. L. Forsberg, Concord  
 Andrew L. MacMillan, Concord  
 Francis Brown, Henniker  
 John W. Blaisdell, Epping  
 Donald W. Leonard, Exeter  
 Fred Fernald, Nottingham  
 Raymond R. Perreault, Rochester  
 B. Read Lewin, Claremont

The necrologist then presented the following report:

#### *Report of the Necrologist*

The following members of the New Hampshire Medical Society have died since the last report of the necrologist:

NAME	DATE OF DEATH	PLACE
Black, James S	April 21 1947	Nashua
Claggett, Fred P	July 4, 1946	Newport
Fox, George L.	November 3, 1946	Exeter
Greeley, Philip H	December 2 1946	Concord
Kendall, Anton H	November 9, 1946	Walpole
Michou, Nicholas D	March 21 1947	Manchester
Sanders, Loren A.	April 29, 1946	Concord
Sprague, Fred A.	December 3 1946	Concord
Thibodeau, Edgar J	January 15 1947	Berlin
Wiggin, Henry M	June 29 1946	Whitefield

Dr MacMillan, for the Committee on Officers' Reports, moved that the report of the necrologist be accepted

This motion was duly seconded and was carried

Dr Dye then presented the names of the candidates for president, for which office three names were submitted and voted on by written ballot John A Hunter, of Dover, the present vice-president, Samuel Fraser, of New Boston, and Edward R B McGee, of Berlin

The President moved that nominations be closed

This motion was duly seconded and was carried

The Speaker appointed Drs Dube and Dinerman to act as tellers

The voting then took place, and the tellers reported that Dr Hunter had received 19 votes out of 20

The Speaker then declared Dr John A Hunter duly elected as president for the ensuing year

Dr Dye presented the following nominations for vice-president Clarence E Dunbar, of Manchester, Harry T French, of Hanover, and Robert W Holmes, of Keene.

The voting then took place, and the tellers reported that Dr Dunbar had received 15 and Dr French 5 votes

The Speaker declared Dr Dunbar duly elected as vice-president for the ensuing year

Dr Dye then read the rest of the slate of officers and committees to serve for the ensuing year

The Secretary called attention to an error made by the Chairman of the Committee on Constitution and By-Laws, who had re-elected the Secretary The Secretary had been elected last year under Article 8 of the Constitution, which says that the Secretary-Treasurer shall be elected for a term of five years

Dr Macmillan moved that the nominations be closed

The President moved that the Secretary cast one ballot for the nominations as read

This motion was duly seconded and was carried

The Speaker then declared the officers whose names had been read as elected for the ensuing year

Dr Lewin, on behalf of the House of Delegates, expressed the appreciation of the House to Lester R Whitaker, president of the Rockingham County Medical Society, and to the President of the Rockingham County Women's Auxiliary, for the fine hospitality they had shown at the first meeting in

Rockingham County since 1927 He moved that this note be added to the minutes of this meeting

This motion was duly seconded and was carried

Dr Parsons presented the name of Dr Louis Marcoux for life membership

This motion was duly seconded and was carried

Dr Leonard stated that, at a meeting of the Rockingham County Medical Society, considerable discussion about the fees for relief cases had taken place He wondered if an expression of opinion might be enlightening to the Committee on Medical Economics in some way so that they might consider the matter

Dr Perreault replied that, at the last meeting of the Strafford County Medical Society, the same opinion had been unanimously expressed and that the delegate had been instructed to present this matter to the House of Delegates The belief was that there was no reason why the doctors should take a cut in their fees, when the druggists, the dealers in coal, fuel and so forth had not taken a cut.

Dr Lewin referred to a similar discussion in Sullivan County and to a talk with the county commissioners regarding county work He hoped that the commissioners had received a picture of the situation, they were considering the old Blue Cross fees for relief cases

Dr Parsons observed that Coos County had also brought this up at its meeting and that, last year, they had presented the same proposal but, instead of having the fees raised, had been given a schedule that was even less

Dr Dinerman referred to a resolution that was passed at the meeting of the House of Delegates in Manchester, with a schedule of Blue Cross and Blue Shield fees to be called to the attention of the Commissioners of Public Welfare, with the recommendations that these fees be the accepted fees He saw no objection to passing a resolution, but he wondered whether physicians were any nearer to getting what they wanted

The President mentioned the necessity of direct contact with the Commissioners of Welfare A resolution would have little effect.

Dr Leonard asked if the Committee on Medical Economics had not already been appointed to take care of such matters

The Speaker replied that the specific duties of the various committees were not very accurately defined He did not know whether the responsibility would come under that committee or under a special committee of the officers, that would be according to the pleasure of this House of Delegates

The Secretary pointed out that the Society had made a similar effort twice previously, with meetings and conferences with the Board of Public Welfare and all the county commissioners Nothing constructive had been accomplished The chairman of the Welfare Committee had said that he thought that physicians should be willing to take a cut in price because they were getting so much

experience out of these cases. The only solution seemed to be by some form of extra taxation. The motion passed during the previous year had been sent to the Board of Welfare, the motion being that the Society would like to put into effect for these cases the allowances on the Blue Shield schedule, the recommendation was pigeonholed.

Dr. Parsons stated that the points objected to on the fee schedule particularly in Coos County were the \$1 00 fee for complete obstetric care and the facts that mileage was no longer allowed and that only three calls per week at \$1 00 per call were permitted. Dr. Appleton had spoken in Gorham of the fact that he had happened to have one patient in the Berlin Hospital and that he had traveled a round trip of thirty-two miles to the hospital, with no mileage and no depreciation on his car.

Dr. Feiner asked if Senate Bill 86 would take care of the situation.

The Speaker replied that the proposed legislation might help the situation.

Dr. Dye moved that the Committee on Medical Economics include this as one of their functions to let them know all about the Blue Shield, and communicate with the Commissioners of Public Welfare, to see if the same sort of schedule as the Blue Shield could be obtained for the welfare cases.

This motion was duly seconded and was carried.

The Secretary stated that the Society had met in Manchester for a good many years, and that seemed to be impossible at present, except for a one-day meeting, because no rooms for overnight were available. The only solution for the present, at least, seemed to be to pick a summer hotel of this type and have the meeting in June or September, rather than in May. The center of the medical population, of course, was in the southern part of the state, and there were two hotels that were in the convention business on the scale that was needed. One of these was the Wentworth Hotel, and the other was at Bretton Woods. The question arose, therefore, whether one or the other of those hotels should be taken, and which one.

The disadvantage of Bretton Woods was the distance. There was no local committee in Bretton Woods to take care of the details of the meeting, so that it would mean that the group of delegates would have to go up once or twice before the meeting and make the arrangements and break the hotel staff in.

One difficulty about the Wentworth Hotel pertained to the exhibits. Some of them were very heavy, and the owner of the hotel, Mr. Smith, had been disturbed this year for fear that the doctors were going to break up his furniture and ruin his floors by moving in all the two-ton material. He rather questioned whether he wanted the meeting another year, if it would cost him a good deal of painting, revamping and so forth. He would probably be glad to have the doctors another year, if the ex-

hibits were not held or were held on a somewhat more limited scale, cutting out the heavy exhibits, which are apt to break his furniture.

Four or five conventions were signed up for June, 1948. The Secretary had taken the liberty of asking Mr. Smith to reserve tentatively the dates of June 16, 17 and 18, in the event that the Society wished to return next June, it would be a good idea to make reservations in advance rather than to wait until the fall, when the whole month of June would probably be taken up.

Dr. Hunter stated that the exhibitors believed that the delegates had not visited them too frequently anyway and wondered if, in the event that the meeting were held in the same place, it would be possible to eliminate the heavy-weight class and perhaps have the exhibits in the foyer. In that way, there would be fewer exhibits, and certainly the men would see them, or at least go by and give the impression that they were more interested than they had been this year.

Dr. Kennard stated that the exhibitors wished the delegates to visit them. So far as the Society was concerned, one of the chief reasons, of course, for having them here was the economic advantage the exhibitors paid quite well for the expenses of the convention. All bills were not yet in, but the exhibitors would probably net around \$1500, which was something to be considered.

The Speaker called attention to two papers presented on the previous day, starting at 11 15 a.m., which carried the meeting up to lunch time, at 12 30 p.m. The Program Committee could put on one paper at 11 15, which would carry the meeting up to 12 00, and it could be definitely stated on the program that the period from 12 00 to 12 30 was the time for visiting the exhibits.

Dr. Dye moved that the House of Delegates meet at the Hotel Wentworth on June 17 and 18, 1948, and that the question regarding the exhibitors be left to the discretion of the Committee on Scientific Work, the President and the Secretary and their designated agents.

This motion was duly seconded by Dr. Dube and was carried.

The Secretary pointed out that the Hotel Wentworth could not furnish the accommodations for the round-table conferences, only bedrooms being available this year, and the maximum number of people in a bedroom was about twenty. Some of the rooms had been overcrowded on the previous day, with a few people sitting on the floors.

The Speaker suggested leaving that matter to the Program Committee for consideration.

Dr. Dube moved that the meeting adjourn.

This motion was duly seconded and was carried.

Whereupon the final meeting of the House of Delegates was adjourned at 10:00 in the morning.

CASE RECORDS OF THE  
MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*BENJAMIN CASTLEMAN, M.D., *Associate Editor*EDITH E. PARRIS, *Assistant Editor*

## CASE 33431

## PRESENTATION OF CASE

A forty-four-year-old unmarried woman entered the hospital because of abdominal swelling.

The patient had felt perfectly well until one year prior to admission, when she began to look "worn out," and a few months later she began to experience gradually increasing fatigue and anorexia. Four months before admission, she noted swelling of the ankles, and a physician told her that she had sugar in the urine and a "swollen abdomen." One and a half weeks before entry she developed a sore throat, a temperature of 102°F and malaise and had subsequently remained bedridden. Three days prior to admission an abdominal paracentesis was performed, with the removal of 6 liters of fluid. A mild icteric tract of the scleras was noticed at that time. During the previous "year or two," the patient had lost 25 pounds. In the preceding fifteen years, the patient had consumed an average of 3 pints of distilled liquor a week, which she had increased to a pint a day for the past year.

Her father had died of tuberculosis at the age of forty-one years, and a sister of "tuberculous dysentery" at the age of sixteen years.

Physical examination revealed many spider angiomas over the abdomen, chest and arms. There was slight icterus of the skin and scleras. The tonsils were enlarged and boggy, and the pharynx was reddened. The cardiac impulse was felt 1 cm. to the left of the midclavicular line in the fifth interspace, and a Grade III apical systolic murmur was present. The mitral first sound was accentuated. The abdomen was distended, firm and tympanitic, with dullness in the flanks. A fluid wave was present, and a firm, irregular, tender liver edge was palpated four fingerbreadths beneath the costal margin. The spleen was felt two fingerbreadths beneath the left costal margin. There was slight edema of the ankles.

Examination of the blood showed 12.6 gm. of hemoglobin and a white-cell count of 15,000, with 92 per cent neutrophils. Urinalysis revealed a specific gravity of 1.010 and ++ test for albumin, and the sediment contained a moderate number of

white cells and occasional red cells. Repeated stools were guaiac negative. A cephalin-flocculation test was ++++ in twenty-four hours. The prothrombin time was 23 seconds (normal, 19 seconds). A van den Bergh reaction was 4.6 mg. per 100 cc. direct, and 5.8 mg. indirect. The nonprotein nitrogen was not elevated. The blood cholesterol was 156 mg. per 100 cc., with 54 mg. of esters.

An x-ray film of the chest showed homogeneous linear areas of density in both lower-lung fields, more marked on the right. There was a small area of fibrosis in the first interspace on the left. The diaphragm moved well, and the heart was within normal limits in size and shape. A barium swallow disclosed an esophagus of normal caliber, no varices were seen. A plain film of the abdomen showed the tip of the liver to lie at the level of the iliac crest. The tip of the spleen did not appear unusually low. The kidneys were poorly outlined. There was a suggestion of a soft-tissue mass in the pelvis, which may have represented the gall bladder. On a repeated chest x-ray film ten days after admission the lung fields were clear except for several areas of linear density in the left lower-lung field and a linear area in the right lower-lung field. The blood sodium was 115.4 milliequiv., the chloride 88 milliequiv. and the carbon dioxide 17.4 milliequiv. per liter. A prothrombin time done eighteen days following admission was 30 seconds.

The temperature, which had been 101.5°F. on admission, fell on the first hospital day, and after remaining only slightly elevated for a week, rose gradually. The pulse varied from 90 to 135 during the hospital stay. On the fourth day, an abdominal paracentesis produced 4000 cc. of fluid, with a specific gravity of 1.003 and containing 895 red cells and 160 white cells per cubic millimeter, of which 125 were lymphocytes, 25 polymorphonuclears and 10 monocytes. The patient had a slow, steady, downhill course, the dyspnea becoming marked, and the patient semicomatose. Petechial hemorrhages appeared on the conjunctivas, scleras and skin of the arms, and there was some bleeding from the mouth. She died after three weeks of hospitalization.

## DIFFERENTIAL DIAGNOSIS

DR. ALLAN G. BRAILEY: This history leaves no room to doubt that this patient had liver disease of some type. The patient was an alcoholic of at least fifteen years' duration, and although she probably took more liquor than she admitted, she confessed intake accounted for some 1600 calories a day. Yet, during the previous year she had lost 25 pounds in weight, so that in all probability she did not consume much food other than alcohol and a serious protein deficiency must have been present. There is no final agreement regarding whether alcohol produces its harmful effect in liver disease solely by



astinal shadow. The cough persisted and was intermittently productive of sputum, which was thick, yellow and tenacious, but not foul. At about that time intermittent cramping lower abdominal pain and tenesmus developed, and frequent small stools, which sometimes contained blood, were passed. Eight months before entry he was bronchoscoped three times at another hospital and was given penicillin and sulfonamides. He improved, but fatigability prevented a return to work. There was a weight loss of 25 pounds. Three months before admission a barium enema showed an annular constricting lesion in the rectosigmoid region. Proctoscopy revealed a fungating lesion 15 cm above the anal ring. An x-ray film of the chest showed collapse of the left lower lobe, a paramediastinal mass and fluid in the left side of the chest. The symptoms persisted, and he had a feeling of discomfort in the left side of the chest.

The patient's previous health had always been excellent. A brother had died of Hodgkin's disease.

Physical examination showed evidence of weight loss. There was a triangular area of dullness at the left base posteriorly, with diminished breath sounds and tactile fremitus in this area. There were no rales. The liver edge was palpable 1 cm below the costal margin. Fullness was palpable high in the rectum, but no definite mass was felt. A hernia was present on the left above the inguinal ring.

The urine contained a rare pus cell and an occasional red cell but was otherwise normal. The hemoglobin was 9.5 gm, and the white-cell count was 5000. An x-ray film of the chest showed collapse of the left lower lobe with no change when compared to a film taken two months previously. Sputum culture yielded a few alpha-hemolytic streptococci and a moderate growth of *Staphylococcus aureus*.

The hospital course was uneventful. A proctoscopic biopsy of the sigmoid lesion showed adenocarcinoma (Grade II), and a resection and end-to-end anastomosis were done. Bronchoscopy was performed.

#### DIFFERENTIAL DIAGNOSIS

DR W. WILSON SCHIER. My first reaction on reading this case was to obey the scientific principle of parsimony and explain the symptoms of cough, chest pain, hemoptysis, lower bowel obstruction and weight loss on the basis of one lesion — an adenocarcinoma of the rectum with metastases to the lung. With further consideration I think that that is my second reaction as well.

The striking feature is the association of chest symptoms with those of lower-bowel obstruction. The first symptom to appear was the increase in the severity of a chronic cough in a fifty-six-year-old weaver. His occupation suggests no predisposition to any disease. Five months later the persistent

cough became severe, and the patient raised a little blood. I assume from the history that he was hospitalized at about that time. An x-ray film of the chest revealed atelectasis of the left lower lobe. During the same period he also developed obstructive lower-bowel symptoms consisting of intermittent cramping pain and small, frequent, bloody stools. On the last admission a biopsy of the rectal lesion demonstrated an adenocarcinoma (Grade II).

Three bronchoscopies had been performed at the time of the first hospital admission, eight months previously — no report is given, presumably nothing was found. A weight loss of 25 pounds was noted.

The history is comparatively short and consistent with that of a primary carcinoma of the lower bowel, with metastases to the left lung. The metastases may have caused obstruction of the left lower-lobe bronchus by extrinsic pressure from invaded lymph nodes or lung parenchyma.

DR STANLEY M. WYMAN. These chest films taken over a three-month period demonstrate the original collapse of the left lower lobe with the shadow lying behind the left border of the heart. The lung fields show no other evidence of active disease. There is a small area of calcification in the extreme right apex. The left hilus is depressed, and the left upper-lung field shows compensatory emphysema, in keeping with the collapse of the left lower lobe. The grid film shows multiple areas of rarefaction in the left lower lobe consistent with the bronchiectatic cavities seen behind a blocked bronchus in chronic obstruction. The left main bronchus can be traced only to a point just beyond the left upper-lobe branch. No definite mass can be outlined, however. Collapse seems to involve chiefly the apical portion of the left lower lobe, but there is probably some collapse of the base as well. The left costophrenic angle is blunted posteriorly, but no definite fluid is seen. During the period of observation the collapse becomes somewhat more pronounced, but again no definite mass can be outlined. The heart shadow is not remarkable, and no definite destructive lesions are visible in the ribs. The appearance is that of changes in the left lower lobe observed following prolonged obstruction to the bronchus, but no definite tumor is seen.

DR SCHIER. After seeing the x-ray films of the chest I cannot decide any more definitely the type of lesion that this man had. During the course of the hospital stay there was further diminution in the size of the collapsed lower lobe. If this had been a lymphomatous tumor one would expect to see large mediastinal masses. Also, such a tumor would have had a faster course and evidence of spread elsewhere.

The lesion in the rectosigmoid region was operated on at this hospital — probably as a palliative procedure. Another bronchoscopy was also performed here, the results of which are not known. The symp-

toms of chest pain and cough continued. These can be attributed to progressive obstruction of the left lower-lobe bronchus with pneumonitis and bronchiectasis beyond. It is not necessary to assume that a lung abscess was also present. The lack of foul sputum does not rule it out, for the alpha-hemolytic streptococci and the *Staph aureus* were associated with nonfoul lung suppuration. On the contrary, if fusiform bacilli and spirochetes had been present, the sputum would probably have been foul. Pneumonitis or extension of the tumor to the pleura could have caused the chest pain and accumulation of fluid seen in the chest x-ray film on admission. The low white-cell count is difficult to explain in the presence of lung infection.

The diagnosis of the lung disease hinges on the bronchoscopic findings — the obstructing lesion may have been missed on previous bronchoscopies because of surrounding granulation tissue. And it may have been missed here because of that. Primary lung disease cannot be ruled out. An adenoma is unlikely, for 7 out of 8 cases occur in women under forty years of age. This should be compared with carcinoma, in which 3 out of 4 cases occur in men and in which 5 out of 7 are in patients over forty years of age. The incidence of adenoma is 5 to 10 per cent of that of carcinoma, and five-year cures are obtained in over 95 per cent of cases. The five-year curability rate for resectable carcinoma of the lung is around 7 per cent. Other noncarcinomatous tumors of the lung, such as hamartoma and sarcoma, may have been present to cause the symptoms of bronchial obstruction. With these, as with dermoid cyst, I would expect a longer history of pulmonary difficulty.

Chronic lung infections of the granuloma type are to be considered in passing — that is, tuberculosis, fungus infections and syphilis. The last, of course, is extremely rare, and even if the blood Hinton reaction had been positive, I would not seriously consider it in this case. Infectious granulomas of the fungus type in the New England states can be confined to actinomycosis, and in the absence of a longer history, rural life and sinuses in the chest, I shall dismiss that diagnosis along with blastomycosis and histoplasmosis. Tuberculosis is a greater possibility both because of its incidence and because of the age and sex of the patient. The rate of pulmonary tuberculosis in women rises to a peak at the age of twenty-three, whereas in males — although less important at that age — it has a greater and rising incidence from the age of thirty-five on.

In the absence of more definitive sputum reports tuberculosis is still a possibility. Granulation tissue surrounding an endobronchial tuberculous lesion may hide such a lesion as it occasionally does with a primary bronchial tumor.

A noninfectious granuloma — Boeck sarcoid — should receive passing attention although obstructive bronchial lesions are unusual with this disease, and the patient's sex and age do not give this possibility any weight.

In summary, then, although a primary lung tumor or infection cannot be ruled out, I favor the diagnosis of a primary tumor in the rectum, with metastasis to the left lung.

#### CLINICAL DIAGNOSIS

Primary carcinoma of lung

#### DR SCHIER'S DIAGNOSIS

Adenocarcinoma of rectum, with pulmonary metastasis

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of rectum*  
*Squamous-cell carcinoma of lung*

#### PATHOLOGICAL DISCUSSION

DR BENJAMIN CASTLEMAN This patient had two separate cancers: an adenocarcinoma of the rectum and a squamous cell carcinoma of the lung. The latter diagnosis was made from the last bronchoscopy. The patient appeared to be in good condition, and a left pneumonectomy was performed. The specimen showed that the left lower-lobe bronchus was filled with white friable tumor, which had also extended up partially to occlude the lingular bronchus of the upper lobe. Beyond the obstruction the left lower-lobe bronchi were all dilated and thick walled. The surrounding pulmonary parenchyma was completely atelectatic and somewhat fibrous. Microscopically, it showed the chronic pneumonitis of the cholesterol type characteristic of chronic obstruction. Although the tumor had directly extended into two small lymph nodes within the lung, there was no evidence of metastases.

The patient did very well postoperatively, and the latest report, which was made only two months following the pneumonectomy, is that he was up and about and felt quite well.

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## OCTOBER MEETING OF THE COUNCIL

MUCH of today's discussion in medical circles concerns the various aspects of the trend toward the socialization of medicine and the development of prepaid medical care. This is, indeed, one of the major problems that confronts us. A large part of the debate in the Council meeting of October 1 took place over the resolution, already adopted by the Committee on Public Relations, "that the Blue Shield through its employees determine accurately an applicant's yearly earnings before issuing the policy, and secondly, that their earnings be reviewed each year." The cost and the difficulties of such a fact-finding program were pointed out, but a number of councilors had their say before the resolution was finally referred back to committee for further study, as the Executive Committee had recommended.

Progress in the organization of women's auxiliaries, under the experienced guidance of Dr. John F. Conlin, was reported, five districts having already approved the new suffrage. Some discussion took place over the action of the Committee on Public Relations in approving the objectives of the National Physicians Committee, but the report as a whole was accepted by the Council. The report of the Committee on Cancer approving the establishment of a cancer-detection clinic at the New England Deaconess Hospital was ordered tabled.

The Committee to Meet with General Hawley with the view of formulating a Program in Massachusetts for the Medical Care of Veterans and Their Dependents presented a *fait accompli* in the form of a neat contract with the Veterans Administration, already signed, providing for examination, treatment and counseling of eligible veterans in Massachusetts. This report was accepted without debate.

The colossal report of the Committee to Survey Malpractice Insurance in Massachusetts was accepted, and its four recommendations adopted, the report of the Advisory Committee on School Medical Services was referred back to the committee for further clarification.

The Committee to Study Special Hospital Services had labored during the summer and produced an almost unassailable report defining hospital services and medical services and establishing the proper relations between them. These relations will always be subject to change and revision with changing times and changing ideals. The Council recognized this report as covering present conditions and accepted it.

The matter of studying the Society's need of a full-time secretaryship and defining the duties of the Secretary, the Director of Medical Information and Education, and the Executive Secretary was referred to a committee of seven with power to act.

The reports of other committees were informational or self-explanatory.

An invitation from the Worcester District Medical Society to hold the annual meeting of the Society in Worcester in 1949 was accepted and referred to the Committee on Arrangements.

One still carries away from a Council meeting the wish that the functions of the Executive Committee might be better understood and employed. The purpose of the Executive Committee is to process the business of the Society before it is presented to the Council. If the Executive Committee does its work thoroughly and conscientiously, and if the councilors study the report of the committee, much of the debating time of the Council can be put to better advantage.

## EPIDEMIC PLEURODYNIA

ELSEWHERE in this issue of the *Journal* appears a preliminary report of an outbreak of epidemic pleurodynia that occurred in Boston this summer. More than 100 cases clinically consistent with this diagnosis were seen at the Boston City Hospital alone. In addition, many members of the families of the patients are known to have suffered a similar ailment. In retrospect, many physicians will recognize this disease in many of the patients whom they have been called to see during the same period for unexplained febrile illnesses of various sorts. This is particularly true of household outbreaks involving multiple cases in which the illnesses began simultaneously or in rapid succession.

As usual in such epidemics, a number of cases have been confused with acute surgical conditions of the abdomen. Undoubtedly, some patients have been operated on unnecessarily because of the failure to consider epidemic pleurodynia in the differential diagnosis. An appreciable number, however, have been spared such operations at the Boston City Hospital and probably elsewhere because the physicians were aware of the prevalence of this condition. Some cases of this disease in which there were symptoms suggesting central-nervous-system involvement have probably been erroneously labeled benign lymphocytic meningitis or nonparalytic poliomyelitis. The latter disease is a particularly difficult one to differentiate during the summer months when both diseases are prevalent.

In patients with pleural pain or with pain referred to the abdomen, the diagnosis of epidemic pleurodynia should be entertained, and frequent examina-

tion of the chest for the presence of a friction rub should be made. Unfortunately, the diagnosis of this disease can be made only on clinical grounds, and the presence of a friction rub in the absence of pleural effusion or of pulmonary consolidation is the only reliable diagnostic sign now available.

The final report of the present outbreak and the results of attempts by several workers to isolate the causative agent will be awaited with interest.

## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

ALPERT — Louis Alpert, M.D., of Middleboro died on August 17. He was in his forty fourth year.

Dr. Alpert received his degree from Boston University School of Medicine in 1929.

His widow and a daughter survive.

ARKIN — Louis Arkin, M.D., of Sharon, died on October 1. He was in his seventy first year.

Dr. Arkin received his degree from Harvard Medical School in 1904. He was formerly professor of laryngology at Tufts College Medical School and was a member of the staffs of the Beth Israel Hospital and the Boston Dispensary. He was a member of the New England Otolological and Laryngological Society and a fellow of the American Medical Association.

A brother and three sisters survive.

SAFFORD — M. Victor Safford, M.D. of Jamaica Plain, died on June 20. He was in his eightieth year.

Dr. Safford received his degree from Medical School of Maine, Portland in 1893. He was formerly deputy health commissioner and epidemiologist, City of Boston Health Department.

His widow and a sister survive.

## NEW HAMPSHIRE MEDICAL SOCIETY

### DEATHS

DOLLOFF — Charles H. Dolloff, M.D., of Concord died on August 19. He was in his seventy first year.

Dr. Dolloff received his degree from Dartmouth Medical School in 1903. He was appointed superintendent of the New Hampshire State Hospital in 1917. He was a member of the American Psychiatric Association and the New England Society of Psychiatry and was a fellow of the American Medical Association. Two grandchildren survive.

FLYNN — Timothy P. Flynn, M.D., of Lancaster, died on September 1. He was in his fortieth year.

Dr. Flynn received his degree from St. Louis University School of Medicine in 1934. He served for two and a half years in the Army Medical Corps in World War II and was a fellow of the American Medical Association.

His widow, his mother, four children, a brother and two sisters survive.

SANBORN — Mary N. Sanborn, M.D. of Meredith died on September 6. She was in her eighty fifth year.

Dr. Sanborn received her degree from College of Physicians and Surgeons, Boston in 1890.

Two sisters survive.

### NOTE

The following New Hampshire physicians were recently appointed fellows in the American College of Surgeons: John H. Kennard, Manchester; Robert C. Nydegger, Concord; and Daniel J. Sullivan, Nashua.

## MISCELLANY

### MASSACHUSETTS TUBERCULOSIS LEAGUE

WHEREAS in the passing of Dr Robert N Nye the Massachusetts Tuberculosis League has lost an esteemed and most valuable friend as well as a member of its Board of Directors, and

WHEREAS in the passing of Dr Nye the League has lost a worthy representative of medicine and a most co-operative editor of the *New England Journal of Medicine*, therefore

BE IT RESOLVED That the Executive Committee of the Massachusetts Tuberculosis League, in session on September 18, 1947, expresses sincere regret at the untimely passing of Dr Nye, and

BE IT FURTHER RESOLVED that in behalf of the Massachusetts Tuberculosis League this Executive Committee extends sincere sympathy to Mrs Nye and other bereaved relatives, as well as to the associates in medicine of Dr Nye and to his associates in the *New England Journal of Medicine* and

BE IT FURTHER RESOLVED that a copy of these notes be sent to Mrs Nye, to the president of the Massachusetts Medical Society and to the *New England Journal of Medicine*

CLEVELAND FLOYD

President

CURTIS N HILLIARD

Vice-President

ARTHUR J STRAWSON

Executive Director

## NOTICES

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, November 6, at 7 15 p m in the classroom of the Nurses' Residence. The subject "Dizziness and Vertigo," with lantern slides, will be discussed. Dr Madelaine R Brown will be chairman.

### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

On Wednesday, November 12, the Division of Hospital Survey and Construction of the Massachusetts Department of Public Health will hold a public meeting to present the State Plan for administering Public Law 725 (Hospital Survey and Construction Act) in the Gardner Auditorium, State House, Boston, at 2 00 p m. The subjects and speakers are as follows:

Explanation of Public Law 725 — Hospital Survey and Construction Act. Vlado A Getting, M D, commissioner, Massachusetts Department of Public Health.

A Plan for the Administration of Public Law 725 in Massachusetts. Staff members of the Division of Hospital Survey and Construction, including A Daniel Rubenstein, M D, director, Claire F Ryder, M D, epidemiologist, Mr Arthur V Harrington, senior engineer, and Mr William W Wood, survey administrator.

Hospital administrators, local health-department officials and all other interested persons are invited to attend.

### JOHN AND MARY MARKLE FOUNDATION GRANTS

The John and Mary Markle Foundation has announced a new program of "post-fellowship grants" by means of which young scientists with the necessary training to hold regular faculty appointments and to conduct original research are offered an opportunity to start a career in academic medicine. Candidates will be recommended by accredited medical schools in the United States and Canada, which will determine the appropriate salary and academic rank, encourage research by setting reasonable limits on teaching and other nonresearch activities, provide laboratory facilities and, if necessary, make financial contribution to the support of the

work. Regional committees appointed by the Foundation will make the final selection of candidates on the basis of the recommendation of the medical schools. Grants of \$25,000, payable to the co-operating school at the rate of \$5000 annually for a five-year period, will be available beginning with the academic year 1948-49. No fixed number of candidates will be appointed in any year, but it is expected that approximately fifty will receive appointments during the five-year period. Details of the program have been sent to all deans of accredited medical schools, to whom those interested in being considered as candidates should apply for further information.

### NEW ENGLAND EPILEPSY LEAGUE

Announcement of the incorporation of the New England Epilepsy League was recently made by L Sherrill Bigelow, president. This organization is a non-profit, self-supported affiliate of the American Epilepsy League, Inc., which has moved to Chicago. The League is governed by a volunteer board of directors, working in close co-operation with a medical advisory board. The program of the League is primarily one of education and referral. The referral service includes lists of physicians, hospitals and clinics particularly interested in the care and treatment of epileptic patients, special schools for the education of children with seizures, colleges and universities that will accept epileptic students and information on training opportunities for the adult epileptic patient provided by state and private agencies. Medical reprints and articles written on the various phases of problems faced by the epileptic, his family and friends are available to all professional and lay members of the New England Epilepsy League. In addition to the above mentioned pamphlets, Dr William G Lennox's book *Seizures and Seizures* is given each member. The officers of the League are anxious to bring information about new methods of treatment to the physicians of New England, who are urged to call on the League at any time. Communications should be addressed to Miss Esther C Walther, director, New England Epilepsy League, Inc., 50 State Street, Boston 9 (Telephone LA Fayette 2550).

### UROLOGY AWARD

The American Urological Association offers an annual award of \$1000 (first prize of \$500, second prize \$300 and third prize \$200) for essays on the result of some clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals. All interested should write to the secretary, Dr Thomas D Moore, 899 Madison Avenue, Memphis, Tennessee. Essays must be in his hands before March 1, 1948. The first-prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Boston, May 17 to 20.

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, OCTOBER 30

##### FRIDAY, OCTOBER 31

\*9 00-10 00 a m Precautions in Handling Radioactive Materials in Medical Research. Dr Shields Warren. Joseph H Pratt. Dorchester Hospital.

\*10 00 a m-12 00 m Medical Staff Rounds. Peter Bent Brigham Hospital.

##### MONDAY, NOVEMBER 3

\*12 15-1 15 p m Clinicopathological Conference. Peter Bent Brigham Hospital.

##### TUESDAY, NOVEMBER 4

\*12 15-1 15 p m Clinicoradiological Conference. Peter Bent Brigham Hospital.

##### WEDNESDAY, NOVEMBER 5

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater. Peter Bent Brigham Hospital.

\*2 00-3 00 p m Combined Clinic by the Medical Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

\*Open to the medical profession.

(Notices continued on page x1)

# The New England Journal of Medicine

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## THE DIAGNOSTIC AND THERAPEUTIC VALUE OF LIVER BIOPSIES\*

With Particular Reference to Trocar Biopsy

WADE VOLWILER, M.D.,† AND CHESTER M. JONES, M.D.‡

BOSTON

ACCURATE information regarding the particular phase of any morbid process under observation is essential to the institution of adequate therapeutic measures. Such an obvious and desirable goal, until recent years, has been only vaguely obtainable in intrahepatic disease. Numerous liver-function tests of simple or complex nature have been devised but have proved useful primarily as a means of estimating the degree of functional damage and of following the progress of intrahepatic disease rather than as a measure of exact diagnosis. The multiplicity of the liver's functions and its notable reserve capacity are such that at best, even when the entire battery of laboratory studies is employed, an imperfect set of findings is obtained. This statement is not to be interpreted as underestimating the various tests of hepatic function, which have a distinct but limited value.

For these reasons various investigators have made an effort to obtain exact histologic information by means of liver biopsy. We also have been interested in a careful histopathologic study of liver disease and have found, as others have, that such knowledge is frequently vital in making correct clinical decisions regarding the differentiation of intrahepatic and extrahepatic biliary obstruction, the type of intrahepatic disease present, the stage of a known intrahepatic disease, the specific therapeutic program to be followed and the appraisal of a therapeutic regime. To justify the practice of liver biopsy, it is necessary to satisfy the following conditions: the procedure must present no undue risk to the patient, and the material so obtained must be adequate for careful histologic examination.

In general, all three of the present-day methods (laparotomy with small incision under local anesthesia, peritoneoscopy and needle biopsy) fulfill both these requirements. Laparotomy is usually

unjustified if either of the two other procedures is available, since the discomfort to the patient is as great as that in the usual peritoneoscopy and the abdominal-wall incision is necessarily much larger. The area of hepatic tissue grossly visualized in such a laparotomy is, of course, considerably less than that seen through the peritoneoscope. In terms of time and money, the expense to the patient is greatest for laparotomy and least for trocar biopsy.

Peritoneoscopy is a painful procedure, and it is therefore difficult to induce a patient to have a second or third examination to obtain material useful in following the progress of intrahepatic disease. In diffuse liver disease, a peritoneoscopic biopsy is often inadequate in its sampling of tissue, and when there has been intrahepatic scarring, the specimen may consist chiefly of liver capsule. Peritoneoscopy should be chosen as a rule when a search for a focal lesion—for example, a neoplasm—is necessary. Even in diffuse intrahepatic disease gross visualization of the liver at times adds important information to that obtained histologically; often, this can all be accomplished by a single peritoneoscopic examination. This procedure also enables the operator to coagulate electrically the site of biopsy if much bleeding is seen. The use of an exterior biopsy needle combined with peritoneoscopy<sup>1, 2</sup> seems unnecessarily elaborate except in unusual circumstances.

Needle biopsy of the liver, when properly performed, usually causes little discomfort and, if a fairly uniform pathologic process is present, provides a satisfactory sampling of tissue from deep within the liver substance. The development of this method has previously been adequately discussed.<sup>3-6</sup> If the liver is markedly enlarged, an attempt to obtain a specimen of suspected metastatic neoplasm by needle biopsy is often reasonable, but failure to find it by this blind method in no way rules out that diagnosis. In coarsely nodular, "toxic cirrhosis," a needle biopsy may fail to include scar tissue although the specimen is seemingly sufficient in amount. Trocar biopsy of a liver that is

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†Assistant in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital.

‡Clinical professor of medicine, Harvard Medical School; physician, Massachusetts General Hospital.

considerably smaller than normal is, in our experience, uncertain and unsafe, nor should a biopsy needle be thrust blindly across pleural or peritoneal planes when focal suppuration is suspected. Chronic passive congestion of the liver may contraindicate liver biopsy, although we have obtained without untoward incident a trocar biopsy in 4 such cases and Sherlock<sup>7</sup> reports 25 cases.

### METHOD

Experience has indicated that, if proper biopsy material is to be obtained consistently, a special kind of needle is necessary. Of the various types of biopsy needles used at present, one is about as satisfactory as another if the operator is experienced and skillful. For the study of most hepatic disorders, we have chosen to use an American modification of the Iversen-Roholm needle, known as the Franseen biopsy needle,\* because it seems to be the simplest effective apparatus available for this purpose. It differs from the original one described by Iversen and Roholm<sup>9</sup> only in that the three sharp points have been fully developed into three sharp teeth. We use the No. 14 gauge size, 11 cm. in length.

The biopsy is performed at the bedside with the patient lying flat on his back, the anterior approach is used. The skin is prepared with alcohol and iodine, and a sterile sheet with a central hole is placed over the chosen area. After a skin wheal has been made with novocain, the thoracic or abdominal wall down to and including the peritoneum is rapidly anesthetized while the patient holds his breath in the phase of respiration chosen for the biopsy. A 0.3-cm. skin nick is made with a sharply pointed Bard-Parker blade. The patient hyperventilates a few times and holds his breath while the biopsy is being done. The biopsy needle, stylet in place, is quickly pushed through all layers of the abdominal wall to the surface of the liver capsule. The stylet is withdrawn and the needle shaft rapidly advanced within the liver substance for a vertical distance of 3 or 4 cm. Suction is then applied to the end of the needle with a 20-cc. syringe having a metal adapter. With the suction in place, the needle and syringe together are quickly withdrawn. As this is done, the tissue obtained usually slides up the needle shaft into the barrel of the syringe, and immediately 10 cc. of physiologic saline solution is aspirated into the syringe to prevent a blood clot from forming around the biopsy specimen. The tissue is then transferred to the fixative.

The actual biopsy maneuvers must be accomplished within ten seconds to allow the patient to hold his breath and lie immobile, otherwise, a liver tear is possible. Overbreathing to achieve a period of spontaneous apnea helps the patient fulfill this requirement. We believe that there should be no fixed rule concerning the site of biopsy, which should be chosen by the operator in each case according to the

physical examination. By the anterior approach, if the liver is enlarged, either the right or the left lobe may be chosen, provided a 5-cm. margin of safety lies between the site of biopsy and the lower liver edge. If the lobe is sharp-edged and thin, the needle should be pointed obliquely cephalad to prevent puncture of organs on the opposite side. An appreciable ascites should be tapped prior to the procedure. If the liver is only minimally enlarged or is of normal size, it is unsafe to attempt biopsy below the costal margin. In such a case, one may proceed with care transpleurally in the anterior axillary line through the intercostal space during expiration. The space usually chosen by us is the first or second below the top level of liver dullness. We prefer to risk going too high rather than too low since, if the patient is immobile, no harm results from puncturing the lower thin edge of lung.

The patient must be alert and co-operative. The prothrombin time must be carefully checked and should be within normal limits or only slightly prolonged. In unusual cases, a freshly drawn, citrated whole-blood transfusion may be given just prior to the biopsy to reduce temporarily an elevated prothrombin time that has been resistant to parenterally administered vitamin K derivatives. An intramuscular injection of one of these derivatives should be given routinely two hours before the biopsy, regular prebiopsy cross matching for possible later transfusion seems unnecessary.

Pain following needle biopsy is highly variable and unpredictable. It is undoubtedly due to irritation of the serous surfaces by extravasated blood. Biopsies done by the trocar method under direct observation at laparotomy produce from 5 to 20 cc. of blood from normal livers. Pleural pain is almost always present after the use of the intercostal approach, but it is usually not severe after the first half hour. It is considered wise to give parenteral Demerol and an oral salicylate routinely half an hour before the biopsy. The patient should lie quietly in one position for the first hour following the procedure, and should stay in bed for the subsequent twenty-four hours. The return of pain after ambulation is a warning sign of probable further oozing of blood from the biopsy site, and if this occurs the patient should immediately return to bed for at least twenty-four hours longer.

### RESULTS

We have attempted needle liver biopsy by this method 234 times in 191 different patients. Of these, 216 biopsies, obtained from 174 patients, provided tissue sufficient for adequate histologic appraisal. In 5 cases focal lesions were missed by an apparently satisfactory biopsy. Sixty-eight biopsies were performed transthoracically in patients with livers of normal size. Thirty-two patients were examined serially with from 2 to 6 biopsies each during the course of therapy. The distribution of pathological

\*Manufactured by Randall-Fairchney Corporation, Boston.

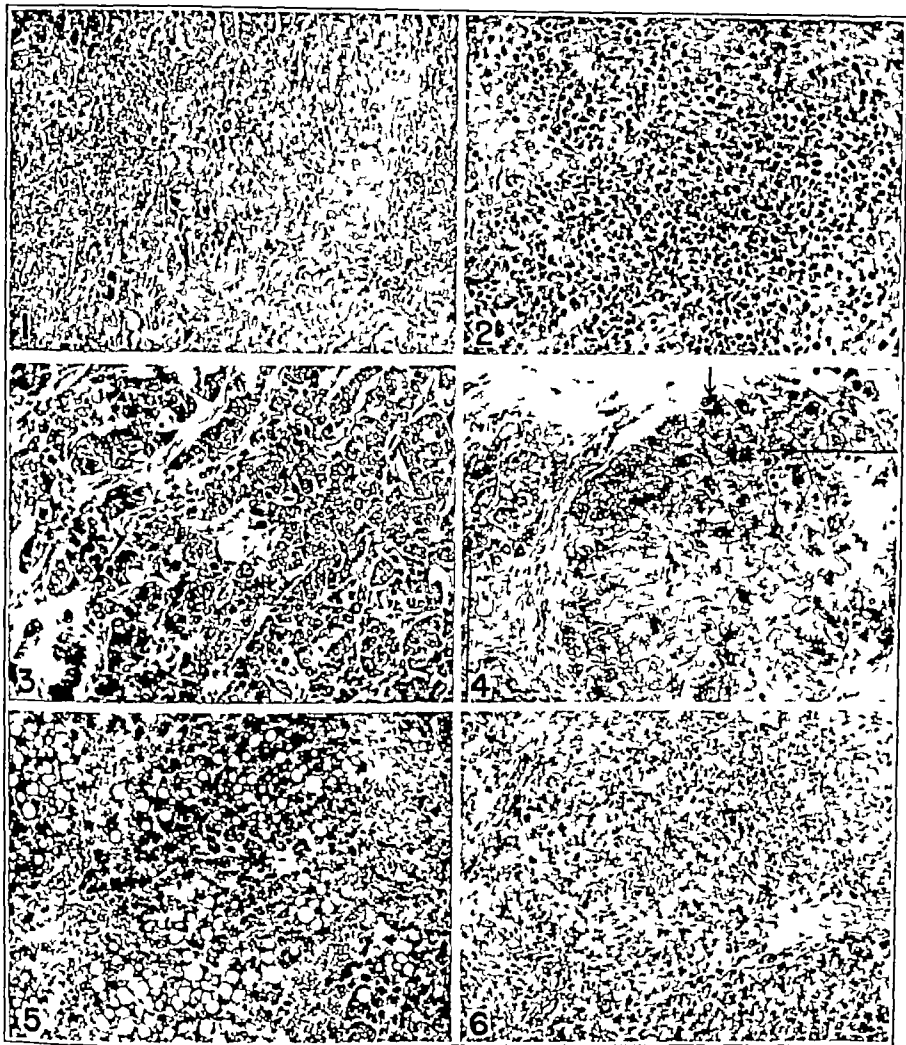


PLATE 1

FIGURE 1. Case 1

Note the lymphocytic infiltration of the portal areas characteristic of epidemic infectious hepatitis.

FIGURE 2. Case 2

Malignant lymphoma infiltrating the liver lobule.

FIGURE 3. Case 3

Adenocarcinoma suggestive of hepatoma.

FIGURE 4. Case 4

Iron stain showing intracellular hemosiderin granules of hemochromatosis.

FIGURE 5. Case 5

Acute degenerative cirrhosis. Note the marked fat vacuolization of the parenchymal cells and the severe leukocytic infiltration.

FIGURE 6. Case 5

Biopsy obtained 3 weeks later than that shown in Fig. 5. Note the normal appearance of the parenchymal cells with disappearance of fat and the marked decrease in polymorphonuclear infiltration.





diagnoses in this series is shown in Table 1. Most of the unsuccessful biopsy attempts occurred in patients with ascites that had not been tapped, or in cases of far-advanced fibrosis in which the suction was apparently insufficient to extract the laterally severed tissue from its base.

One death from uncontrolled hemorrhage followed trocar liver biopsy. In this case the biopsy of a large amyloid liver was accomplished with ease while the patient lay immobile. Hykinone had been given parenterally before biopsy. The prothrombin time was 6 seconds prolonged, which is the arbitrary limiting value chosen by us for this procedure. Ten hours later the patient was found in shock after several hours of severe abdominal pain. Post-mortem examination two days later showed that the needle had pierced the right main hepatic vein 4.5 cm from the surface of the capsule. Intrahepatic bleeding appeared to have created enough pressure to split the friable, superficial amyloid liver tissue, forming a huge laceration extending the entire vertical length of the right lobe. This rent had extended much farther during the twenty-four hours after fibrin foam packing at surgical laparotomy.

One patient died with peritonitis that was possibly attributable to the biopsy procedure. This man, with a fulminating acute cirrhosis, was found at autopsy to have a beta-hemolytic streptococcus peritonitis and septicemia. The pathologist stated that this infection appeared to be of three to ten days' duration. The temperature chart and clinical data provided no clue to the time of its onset. The biopsy had been performed five days before death. Since this experience, all biopsy instruments have been carefully autoclaved as complete sets. We believe, however, that this death was not attributable to aspiration biopsy.

Moderate bleeding after biopsy was observed in 3 other patients, in all of whom the prothrombin time was normal, none required transfusion. Two patients bled intra-abdominally, accumulating a detectable ascites, and 1 developed a large abdominal-wall hematoma without intraperitoneal bleeding. One of those with intraperitoneal bleeding had a highly vascular metastatic carcinoma, the other had shown a slight hemorrhagic tendency, not related to platelet or vitamin C lack, but had been given a fresh whole-blood transfusion just before the biopsy.

### CASE REPORTS

The following cases illustrate the value of liver-biopsy material in providing correct diagnoses, in determining the phase of a given hepatic disorder actually present and in appraising the results of a therapeutic program in patients with diffuse liver damage.

**CASE 1.** A thin, tired 48-year-old man was hospitalized for study of painless, pruritic, deep jaundice that had been present for 3 weeks. This had been preceded by 3 months of increasing fatigue and a weight loss of 20 pounds without gastrointestinal symptoms. No history of alcoholism was obtainable. The jaundice had been accompanied by light stools and dark urine. A slightly enlarged, nontender liver was palpable. No splenomegaly, spider angiomata or abnormal fluid retention was demonstrable. A ray film of the chest and upper gastrointestinal tract were normal. During the 1st week of hospitalization the stool varied irregularly from clay colored to light brown. One stool was strongly guaiac positive. Two sets of blood chemical studies a week apart were almost identical in values including a total serum bilirubin of 40 mg. per 100 cc., a serum alkaline phosphatase of 9 Bodansky units and a total cholesterol of 255 mg. per

TABLE 1 Diagnoses Revealed by Trocar Aspiration Liver Biopsy

DIAGNOSIS	NO. OF PATIENTS	DIAGNOSIS DETERMINED BY BIOPSY
Fatty infiltration	15	12
Portal cirrhosis	57	5
Hemachromatosis	4	4
Bile stasis	1*	6
Biliary cirrhosis	5	2
Infectious hepatitis, acute	16	1
Infectious hepatitis, chronic	10	2
Amebic hepatitis	2	0
Lipomatosis	4	4
Metastatic carcinoma	9	9
Malignant lymphoma	1	1
Alcoholic leukemia	1	1
Amyloid infiltration	1	1
Chronic passive congestion	2	0
Sarcoid	2	2
Normal liver clinically thought abnormal	22	22
Miscellaneous*	7	6
<b>Totals</b>	<b>171</b>	<b>79</b>

\*Includes 1 case of central necrosis, 1 of focal degeneration, 3 of unclassifiable hepatitis, 1 of carbon tetrachloride hepatitis, 1 of schistosomiasis and 1 probable case of cardiac cirrhosis.

100 cc. with normal figures for prothrombin, thymol turbidity and flocculation, cephalin flocculation, albumin and globulin.

Because metastatic carcinoma was strongly suspected, a peritoneoscopy was performed. No focal lesions were seen. The specimen obtained on liver biopsy was typical of epidemic infectious hepatitis, which had not been suspected from the clinical and laboratory data (Fig. 1). In this case an exploratory laparotomy that might have impaired or greatly retarded the patient's recovery was avoided.

**CASE 2.** A drowsy, well nourished 69-year-old man presented a history of an acute painless illness of 3 weeks duration, initiated by abdominal distention and vague indigestion. This was followed in 2 weeks by nausea, vomiting, fatigue and dark urine. Three days before entry frank jaundice had appeared.

Moderate icterus and a large symmetrical slightly tender liver were the only abnormal physical signs present. The stools were brown.

Laboratory studies included a cephalin flocculation test, which was +++ in 24 hours, a serum alkaline phosphatase of 12 Bodansky units per 100 cc. and a positive test for urinary urobilinogen in a dilution of 1:512.

Some observers believed this to be a fulminating acute epidemic infectious hepatitis, superimposed on a large, fatty or cirrhotic liver although no reliable history of alcoholic intake could be extracted. Others held that such a tremulous, firm liver ought to be filled with neoplasm. A needle biopsy of the liver demonstrated a malignant lymphoma (Fig. 2).

At post mortem examination this process was seen to be localized to the liver, vertebral bone marrow and mesenteric lymph nodes. A correct ante-mortem diagnosis could have been made only by liver biopsy.

**CASE 3** A cachectic, 63-year-old man had been seen in the outpatient clinic 6 weeks before admission complaining of migratory bone and joint pains. A careful and complete physical examination at that time had been negative. X-ray films of the chest and various bones were normal. Two weeks before entry, there was a rapid onset of ankle edema, chest and back pain and alternate constipation and diarrhea.

Physical examination showed fluid in the right pleural cavity, ascites, peripheral edema and hepatomegaly. X-ray films of the colon, upper gastrointestinal tract and kidneys were normal. It was assumed that widespread metastatic neoplasm was present. A peritoneoscopy was performed by Dr Edward B. Benedict, whose report was as follows:

The surface of the left lobe is smooth, with a slightly rounded edge and a 0.5-cm lesion on the lower part of the anterior surface. This lesion may be metastatic carcinoma but could be fibrosis. The right lobe is smaller than the left, a little more irregular and slightly granular, with a more rounded edge. There are no areas on the sur-

and that for 17-ketosteroid urinary excretion showed 18 mg in 24 hours.

X-ray films revealed no esophageal varices. A skin test with acidified potassium ferrocyanide solution and two skin biopsies were negative for hemachromatosis. A trocar liver biopsy showed definite hemachromatosis (Fig 4).

The patient returned to the hospital 1 month later in cardiac failure and died, and autopsy disclosed hemachromatosis of the liver, pancreas, adrenal glands, lymph nodes, thyroid gland, pituitary body and heart. Esophageal varices were also present.

Liver biopsy was essential for a correct clinical diagnosis in this case.

**CASE 5** A middle-aged man was admitted to another hospital\* because of chronic alcoholism of 3 years' duration. For the 3 weeks before entry he had ingested little food but considerable alcohol. When completely sober, he maintained that he had no symptoms of any physical illness what-

TABLE 2 Laboratory Data in Cases 6, 7 and 8

CASE No	SERUM BILIRUBIN		BROM-SULFALEIN RETENTION*	CEPHALIN FLOCCULATION		SERUM ALBUMIN	SERUM GLOBULIN	ALBUMIN GLOBULIN RATIO
	DIRECT mg/100 cc	INDIRECT mg/100 cc		AT 24 HR.	AT 48 HR.	gm/100 cc	gm/100 cc	
6	0.9	1.3	50	++++	++++	2.31	3.50	0.65
7	Normal	Normal	34	+	+++	2.58	4.30	0.60
8	0.6	1.2	32	+++	++++	2.95	5.38	0.55

\*Forty-five minutes after administration of 5 mg per kilogram of body weight.

face suggesting carcinoma. In the lower portion of the abdomen on the peritoneal surface of the abdominal wall there are three or four gray-white, irregular areas about 1 cm in diameter that look fibrotic but may be metastatic carcinoma. None of them are sufficiently large or accessible enough for biopsy.

In a biopsy specimen taken from the anterior surface of the left lobe of the liver, the capsule is extraordinarily tough, and it is quite possible that little liver tissue was obtained. It was impossible to take the biopsy from the small lesion where carcinoma was suspected because this area could not be found with the small telescope. The findings are inconclusive. From the size of the liver and the appearance of it, there may be carcinoma inside the capsule that has not yet broken through and is therefore not visible by peritoneoscopy, although there is a slightly suspicious area.

The biopsy so obtained consisted of a small island of normal liver cells.

A few days later a trocar biopsy was obtained from both the right and the left lobes of the liver, each specimen consisted almost entirely of carcinoma, interpreted by the pathologist as suggestive of hepatoma (Fig 3).

It is unusual for a blind needle biopsy to yield neoplastic tissue when the peritoneoscopy has failed to obtain it.

**CASE 4** A 45-year-old man developed progressive hepatic enlargement during the 2 years subsequent to a transient episode of icterus that occurred during antisyphilitic arsenical therapy. He was a frequent imbibor of alcohol.

Physical examination revealed diabetes, a large liver and a slight tan tint to the skin. Splenomegaly, edema, icterus and spider angiomas were absent.

Laboratory data included a negative cephalin-flocculation test, a total serum protein of 6.8 gm per 100 cc, with an albumin of 3.2 gm, a globulin of 3.6 gm and an alkaline phosphatase of 3.2 Bodansky units per 100 cc. The brom-sulfalein test showed 22 per cent retention of the dye in 45 minutes after a dose of 5 mg per kilogram of body weight. The blood electrolytes were normal, a test for follicle-stimulating hormone was positive for 6.5 mouse units in 24 hours,

soever, although the liver was large and the scleras slightly icteric. He was afebrile.

Laboratory data revealed a trace of bilirubinuria and urine urobilinogen detectable in a 1:1500 dilution. The brom-sulfalein test showed 36 per cent retention of the dye in 45 minutes after a dose of 5 mg per kilogram of body weight. The serum bilirubin was 0.8 mg per 100 cc direct and 1.5 mg indirect. The values for serum albumin, globulin, prothrombin, vitamin A, cephalin flocculation and thy mol turbidity and flocculation were normal.

A trocar liver biopsy obtained was described as follows:

There is severe diffuse cirrhosis with unusually marked polymorphonuclear infiltration. Fat vacuolization is of moderate severity and irregularly distributed. The vacuoles are of exceptional size. In a few areas hyaline degeneration is evident (Fig 5).

This severe, acute, degenerative process had been unsuspected by careful clinical and laboratory examinations. Because of the histologic information, the patient was kept under close medical observation and given intensive dietary therapy. A second biopsy was obtained 3 weeks after the first, at which time the liver was only slightly smaller. The patient was still minimally icteric, although bile pigment had disappeared from the urine. The urinary urobilinogen had returned to a normal concentration, the other liver-function tests were essentially unchanged. Histologic comparison of this biopsy with the first showed a marked reparative change to have taken place.

The fat has largely disappeared. The majority of the liver cells now appear normal, whereas few did so in the original biopsy. Polymorphonuclear cells are still present, but markedly decreased in number. The fibrosis remains unchanged (Fig 6).

In the following patients with similar clinical histories, physical findings and laboratory tests, histologic studies of the liver were markedly different. On physical examination the livers were

\*This patient was examined through the courtesy of Dr Joseph Thimann, medical director of the Washington Hospital, Boston, an institution devoted to the treatment of male alcoholic patients.

approximately of the same size, and icterus was not evident. The laboratory data in these cases are presented in Table 2

**CASE 6** A 46-year-old man was admitted to the hospital because of a rapid onset of ascites within a few days. For many years the alcoholic intake had been impressive, and the food intake scant and irregular. Ankle edema had been present intermittently for 6 months.

Physical examination revealed spider angiomas, ascites, ankle edema, splenomegaly and an enlarged firm liver.

A liver trocar biopsy obtained shortly after admission was described as follows:

A definite cirrhosis without fat vacuolization is seen. Many liver cells show pyknosis. Hyaline bodies thought to represent remnants of necrotic liver cells are present. There is moderate lymphocytic infiltration of the portal areas.

This fibrotic inflammatory picture was not considered characteristic of either the usual and expected degenerative cirrhosis associated with malnutrition and alcohol or the epidemic infectious hepatitis due to a virus. A satisfactory pathological classification was impossible.

**CASE 7** A 35 year-old Italian housewife was admitted because of anorexia, weakness and abdominal swelling of 3 months duration. For many months the food intake had been exceedingly poor in quality and small in quantity. The regular daily intake of wine had progressively increased.

Physical examination demonstrated a minimal ascites, a large liver and a palpable spleen.

Needle liver biopsy obtained shortly after admission was reported as follows:

The architecture is obliterated and there is definite cirrhosis. There is abundant fat, a small amount of hyaline degeneration and scattered focal necroses with considerable polymorphonuclear reaction.

This was considered typical of the acute inflammatory degenerative cirrhosis usually associated with malnutrition and alcohol.

**CASE 8** A 45 year-old woman with a prolonged copious alcoholic and poor food intake was hospitalized because of ascites of a few weeks duration. Physical examination showed moderate ascites, a large liver and a smooth red tongue.

Needle liver biopsy revealed a histologically stationary portal cirrhosis with nodular parenchymal cell regeneration and fibrosis, without active inflammation, fatty infiltration or cellular necrosis.

### Discussion

The differentiation of intrahepatic and extrahepatic biliary block in a case of icterus often poses a difficult problem for the clinician. Clinical facts and a complete set of liver-function tests may be initially inconclusive, whereupon one is faced with the choice of three alternatives: immediate exploratory laparotomy, further observation until such time as the diagnosis becomes clinically obvious and liver biopsy by the peritoneoscope or by trocar. Even under local or spinal anesthesia, abdominal exploration often produces a serious exacerbation of an intrahepatic inflammatory process and is to be avoided if possible. During the course of one or two weeks' hospitalization, clinical and laboratory findings may clearly indicate an intrahepatic or extrahepatic biliary block, but in definite drifting without a clinical solution to the problem is undesirable. Biopsy material obtained early in the course of hospitalization will prevent

uncertainty and may save time that is therapeutically valuable, as in Case 1 above.

Biopsy may also provide the only reliable information regarding the kind of intrahepatic disease present, as in Cases 2, 3 and 4. Liver-function tests and clinical data may promptly indicate intrahepatic impairment but may give only a vague idea of its nature. An exacerbation of degenerative cirrhosis with icterus is often mistaken for epidemic infectious hepatitis. Hemachromatosis without diabetes or skin pigmentation may masquerade as ordinary cirrhosis. By liver aspiration biopsy we have found other diseases clinically unsuspected, including amyloid infiltration, sarcoid, lymphoblastoma, aleukemic leukemia and carcinoma. By this method a neoplasm was obtained from deep within both enlarged hepatic lobes in 2 patients in whom peritoneoscopy had failed to demonstrate a surface lesion — Case 3 was one of these, and in the other a biopsy taken at laparotomy had also been normal. Sufficient parenchymal-cell regeneration may occur to compensate fully for a degenerative cirrhosis, so far as laboratory measures of function are concerned, even though the fibrosis present may cause serious portal hypertension. When laboratory function tests are completely normal, biopsy alone will solve the cause of hepatic enlargement.

If one is to know accurately the phase of a recognized diffuse intrahepatic disease (with the exception of simple, acute epidemic virus infectious hepatitis), liver biopsy is usually necessary. In prolonged, chronic epidemic infectious hepatitis, liver-function studies may give only a rough idea of the degree of active inflammation, cellular degeneration and fibrosis present.<sup>10</sup> Severe, acute "alcoholic cirrhosis" may exist without notable symptoms or marked derangement of laboratory and liver-function tests, as in Case 5. All cases of cirrhosis do not present a uniform histologic picture. Striking differences in the degree of cell necrosis, inflammatory reaction, fat vacuolization, fibrosis and liver-cell regeneration may be seen in patients with identical clinical findings and liver-function tests (Cases 6, 7 and 8). In such cases the immediate clinical response to be expected from strenuous therapy and the long-term prognosis may be indicated by the histologic state of the liver at the time treatment is instituted. Obviously, little improvement can be expected with an end-stage, stationary histologic picture, such as that in Case 8, whereas a far better prognosis is indicated by the active processes of reparative regeneration usually observed in the acute degenerative fatty livers associated with alcohol and malnutrition (Cases 5 and 7).

Liver biopsy material may provide, in addition, important indications for a specific therapeutic program. Supplements of lipotropic substances will be used with considerable more enthusiasm if appreciable fat vacuolization of the hepatic cells is observed, particularly if it is present after a pro-

longed and adequate dietary regime has been followed. Since the severity of active intrahepatic necrosis and inflammation often does not correlate with the clinical impression, as in Cases 5, 6, 7 and 8, in chronic infectious hepatitis of long duration and in degenerative cirrhosis, the obtaining of biopsy material may sometimes show the necessity for a more intensive and careful therapeutic program than would otherwise be pursued. In considering the propriety of a Blakemore surgical attack on portal hypertension by venous anastomosis in a patient with cirrhosis, a study of liver histology is desirable to rule out active intrahepatic degeneration. Its presence increases the operative risk and demands a preoperative preparation of several weeks' dietary treatment. On the basis of a diagnostic liver biopsy, specific therapy may be determined for conditions such as kala-azar, schistosomiasis, tuberculosis, syphilis, leukemia and lymphoma.

Finally, in certain types of diffuse intrahepatic disease, biopsy material is absolutely essential to accurate appraisal of the results of a therapeutic program. As a supplement to clinical and laboratory information, histologic data are particularly necessary in evaluating the various methods of treating degenerative cirrhosis and fatty liver. During the course of treatment of an acute exacerbation of cirrhosis, laboratory tests frequently give a false impression of the phase of the degenerative inflammatory process actually present, as in Case 5 above. In the face of unchanged, poor hepatic function, as measured by serial laboratory examinations, a satisfactory decision regarding when to mobilize the patient and cease heroic care may depend on biopsy findings.

In our experience, the needle aspiration biopsy method described above has been satisfactory for obtaining an optimal sampling of liver histology in patients with diffuse hepatic disease. By this procedure, trauma and maceration of the biopsy tissue have rarely been troublesome. Its very simplicity encourages its wide application as a tool for the study of abnormal physiology in disease of the human liver and as a method for making exact pathological diagnoses. To a large degree, the risk will depend on the experience and judgment of the operator and on the accuracy of the physical examination, not all patients are suitable candidates. Our mortality to date (0.5 per cent), our minimal incidence of other complications and the mortality for other published trocar liver biopsy series<sup>5, 7</sup> compare favorably with reported peritoneoscopic statistics<sup>11-13</sup> for which Benedict<sup>11</sup> estimates the mortality should be less than 1 per cent. It is believed that the value of the histologic information to be gained by needle aspiration biopsy more than justifies the small risk involved.

## SUMMARY

The technic and indications for use of needle aspiration liver biopsy are described.

We have performed 234 such procedures with 0.5 per cent mortality. Of the total number, 216 provided sufficient tissue for adequate histologic appraisal, in 79 cases the biopsy was essential to an accurate clinical diagnosis.

It is believed that aspiration liver biopsy will furnish the following practical information: correct differentiation of extrahepatic and intrahepatic biliary obstruction when clinical and laboratory data are inconclusive, exact diagnosis of the type of diffuse intrahepatic disease, determination of the particular phase of a known subacute or chronic hepatitis present, indications for therapy not obtainable from complete clinical and laboratory examinations, and accurate evaluation of therapeutic regimes in certain types of chronic hepatic disease.

In our experience, needle aspiration liver biopsy has proved a useful and safe measure for making exact diagnoses and for studying the abnormal physiology of liver disease.

Since this report was submitted for publication, we have attempted needle aspiration biopsies of the liver in 44 additional cases, in 43, satisfactory tissue specimens were obtained. Three further nonfatal complications were encountered: massive intra-abdominal hemorrhage requiring transfusion occurred in a patient with a normal prothrombin time (autopsy many weeks later disclosed a large subcapsular hematoma of the liver), during a transpleural biopsy approach, 15 cc of clear bile was aspirated from a gall bladder, but no liver tissue was obtained — recurrent pain and fever during the subsequent ten days, indicating a mild right upper-quadrant bile peritonitis, subsided spontaneously, and atelectasis of the lower lobe of the right lung occurred one day after biopsy of an enlarged liver through an abdominal approach — this pulmonary collapse was presumably produced by splinting of the right leaf of the diaphragm because of severe pain following the biopsy.

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## RENAL DAMAGE FOLLOWING INTRAVASCULAR HEMOLYSIS\*

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THE sequence of hemoglobinuria followed by oliguria and anuria is well known. The observations reported below are especially concerned with the medical management of the anuric patient and with the functional and anatomic reversibility of the renal lesion produced.

In the case of anuria following massive intravascular hemolysis reported below, the patient recovered from the episode only to succumb three months later to homologous serum hepatitis. During the intervening period, the renal function showed steady improvement as evidenced by clinical and laboratory tests. Autopsy offered a unique opportunity to correlate the residual anatomic lesions with the clinical picture. In a review of the literature, no similar observation was encountered, the pathological data reported being limited to the acute phase of the condition.

## CASE REPORT

B. H., a 29-year-old housewife was admitted to the hospital because of anuria. During the week prior to admission an abortion had been performed at the 4th or 5th month of pregnancy, and the patient subsequently had vaginal bleeding. Three days before entry it was noted that she was pale and that the skin was "bronzed." She became weak and delirious, and was taken to another hospital, where she was unresponsive and apparently in shock. The red-cell count was recorded as 750,000, and the blood was Type A and Rh+. No difficulty was encountered in typing or cross matching, but it was noted that the patient's blood was badly hemolyzed. A 500-cc. transfusion of Group A Rh+ blood was given. Since the patient had not voided since admission, she was catheterized several hours after completion of the transfusion and 30 cc. of dark-brown urine full of amorphous material was obtained. She was then transferred to the Peter Bent Brigham Hospital.

There was no history of nephritis or any indication of previous renal damage. The patient had had an earlier pregnancy resulting in a full-term normal delivery of a healthy male infant 10 months prior to admission. There was no past or family history of anemia, jaundice or blood disorder.

Physical examination disclosed a delirious and unresponsive patient. The face was puffy, and there was a bluish-brown tint to the skin. The sclerae were dull and questionably icteric. There were several hemorrhages in the fundi. The mucous membranes were exceedingly pale. Examination of the chest was negative. The heart was normal in size, and the rate rapid and regular, with occasional extra systoles and a Grade I apical systolic murmur. The abdomen was slightly distended. The liver and spleen were not palpable. The legs showed barely perceptible edema. Neurologic examination was negative. Pelvic examination revealed a soft boggy cervix with a widened os and some discharge from it. The uterine fundus was two or three times the normal size. There were no adnexal masses.

Examination of the blood revealed a hemoglobin of 4.4 gm., with a hematocrit of 10 per cent, and a white-cell count

of 41,900 with 76 per cent neutrophils, 15 per cent young granulocytes, 4 per cent lymphocytes and 5 per cent monocytes. There were marked spherocytosis (Fig. 1) and anisocytosis and a reticulocyte count of 5.1 per cent. The fragility of the red cells to hypotonic saline solution was increased. The platelets appeared normal on smear. The serum was dark reddish brown in appearance and on the following day contained 222 mg. of hemochromogens per 100 cc., most of which was in the form of free hemoglobin (Table 1). A blood Hinton test was negative. Twenty cubic centimeters of urine obtained by catheterization was reddish brown, with a reaction of pH 7.5. The urine showed a +++ test for protein, no sugar and a positive test for bilirubin and also for hemoglobin, and the sediment contained rare red cells, many white cells and a large amount of amorphous material.

The blood urea nitrogen was 170 mg., the nonprotein nitrogen 270 mg. and total protein 6 gm. per 100 cc. with 3 gm. of albumin and 3 gm. of globulin. The fasting blood sugar was 131 mg. per 100 cc., and the carbon dioxide combining power was 15.2 and the blood chloride 110 milliequivalents per liter. No sulfonamide was detected in the blood. A stool was watery, brown and guaiac negative.

The serum was found to contain agglutinins for all Rh+ cells, and autoagglutination was observed with the patient's own cells and serum. Consequently all transfusions given were Rh- and there was no evidence of reaction to any of them.

During the first 6 days the patient was given considerable quantities of whole blood plasma, isotonic saline solution and glucose intravenously, as well as penicillin for the pelvic infection and digitalis as prophylaxis against the development of heart failure and pulmonary edema. Within 48 hours she became more lucid, and she was rational after the 3rd day. The blood urea nitrogen continued to rise, however, and the urinary output averaged below 100 cc. daily through the 9th day. Nausea and vomiting persisted. With the development of edema and bilateral hydrothorax on the 6th day fluids were temporarily restricted.

On the 10th day diuresis began, with disappearance of the edema, slow decrease of the blood urea to normal and cessation of the nausea and vomiting. With the exception of an unexplained febrile period during the discontinuance of penicillin between the 23rd and 27th days recovery was uncomplicated. The patient was discharged in good health on the 69th hospital day. The results of renal function tests at the time of discharge and following discharge are presented in Figure 2.

The patient returned 1 month later for further studies. She had felt well in the interval. On the day prior to admission, however, slight right upper-quadrant pain, nausea and vomiting had developed. The sclerae were slightly icteric and the serum bilirubin was elevated.

Even before this admission, several cases of jaundice had been traced to a plasma pool from which this patient had received plasma 3 months previously and the development of hepatitis was anticipated. For 4 days the patient appeared to do well although the prothrombin time fell to 20 per cent of normal and the serum bilirubin climbed to 13 mg. per 100 cc. On the 5th day she rapidly lapsed into coma, dying 48 hours later of homologous serum hepatitis.

Autopsy. Post mortem examination revealed the body of a normally developed and well nourished woman. The skin and sclerae were markedly icteric. The heart and lungs were not remarkable. The liver, which weighed 1050 gm., was the usual shape but flabby in consistence and the capsule was wrinkled; the organ was dull yellow brown. The cut surfaces varied in appearance. Large areas were uniformly pale yellow brown and the lobular markings were indistinct. Elsewhere the sinuoids were accentuated and bright red, and the intervening parenchyma was pale yellow and apparently decreased in amount. There was no dilatation of the

\*The details of this heterogeneous plasma pool have been reported elsewhere and the danger of transmission of homologous serum hepatitis by the use of pooled plasma emphasized.

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bile passages, and examination of the gall bladder and extrahepatic bile ducts was negative.

The spleen weighed 355 gm and was larger than normal, but was of the usual shape; it was soft in consistence. The



FIGURE 1 Smear of Patient's Blood on Admission (Wright's stain)

*This shows several densely staining spherocytes.*

capsule was intact and free from adhesions. Cross sections were red gray, and the malpighian corpuscles were prominent.

The right kidney weighed 140, and the left 180 gm. Both kidneys were similar and of normal shape and size. They

The renal capsule was thin, gray and translucent and could be stripped from the kidney surface with ease. The capsular surfaces of the kidneys were pale brown and uniformly and firmly granular. The cut surfaces were light brown, and the demarcation between the cortex and the medulla was sharp and distinct. The width of the cortex

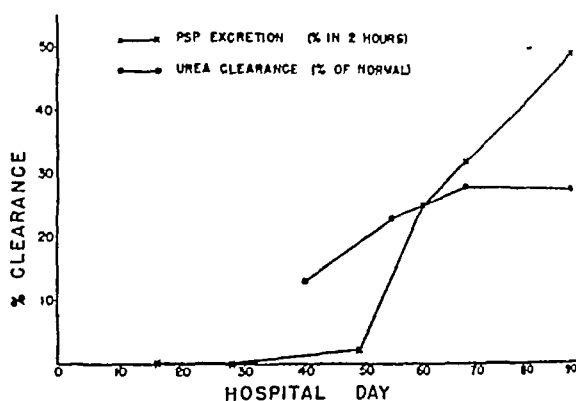


FIGURE 2 Renal-Function Tests

varied between 0.6 and 0.8 cm. The cortical surfaces were mottled, and their markings were indistinct. The pyramids presented the usual appearance. The calyces, pelves and ureters were not remarkable.

Examination of the remaining organs revealed nothing of note.

For microscopical study, blocks of kidney tissue were fixed in Zenker's acetic acid solution and 10 per cent formalin.



FIGURE 3 Photomicrograph (low power) of the Kidney Cortex (phosphotungstic acid-hematoxylin stain). Note the pattern of the scarring.

were surrounded by a moderate amount of perirenal fat, which was not adherent to the capsule. At the hilar region, the vessels and ureters were arranged in the usual manner.

Sections were stained with eosin methylene blue, Mallory's phosphotungstic acid hematoxylin, Mallory's aniline blue and Turnbull's blue stain for iron.

The changes observed on histologic examination were definite but not extensive. There was diffuse subcapsular scarring which frequently formed into narrow radial bands extending deep into the medulla. The fibrous tissue was occasionally pale and edematous. Throughout the scarred areas, particularly in the cortex, occasional small focal collections of lymphocytes were observed. Lymphocytes were also present in the pelvic fat and in the connective tissue beneath the pelvic epithelium (Fig. 3).

The greater number of the glomeruli were normal in appearance. The glomeruli in the scarred areas showed slight pericapsular scarring but were otherwise not remarkable.

Some of the convoluted and more particularly the collecting tubules especially those in the outer zone, were dilated and their lining epithelium was flattened. A few of these tubules contained pale, acidophilic-staining hyaline casts and, rarely, desquamated epithelial cells. The pattern of the involved tubules was such as to suggest the destruction of a nephron or a group of nephrons. By far the greater number of tubules showed no evidence of damage beyond slight cloudy swelling. Brown pigment granules that gave a positive reaction for iron were occasionally found in the tubular cells and throughout the stroma.

The blood vessels showed no visible involvement in either the scarred or the nonscarred areas.

Examination of sections of the liver showed massive destruction of the cells with consequent loss of architecture. The liver cells were shrunken with poorly stained cytoplasm and indistinct nuclear and cell outlines. There was marked polymorphonuclear infiltration about the portal areas and slight infiltration throughout the other areas. The bile ducts were intact for the most part, and in a few areas bile-duct proliferation was noted.

The sinuses of the spleen were engorged by red cells. A few macrophages contained hemosiderin. The malpighian corpuscles were enlarged but were made up of mature cells and they were infiltrated by a few polymorphonuclear cells. There was no increase in fibrous tissue.

Sections of femoral and rib bone marrow were examined. There was marked activity in both the red-cell and the white-cell series. No abnormal forms were noted. Megakaryocytes were numerous.

## DISCUSSION

### Nature of the Hemolytic Reaction

This patient developed a massive hemolytic reaction following an abortion. Although the anemia may have been due in part to bleeding, the dark urine containing blood pigments and the hemoglobinemia, abnormal fragility and spherocytosis of the red cells left no doubt that an acute hemolytic process was still in progress at the time of admission. Spherocytosis has been shown to be an indication of damage to the erythrocyte in various acute hemolytic anemias.<sup>2</sup> Abnormal agglutination and leukemoid white-cell reaction have also been observed in acute hemolytic anemia.<sup>3</sup> All these abnormalities, with the exception of the anemia, disappeared a few days after admission. The diminution of spherocytosis and fragility closely paralleled one another.

The possibility of a hemolytic transfusion reaction in the first hospital seems to be excluded by the bronze skin on admission to that hospital, the hemolyzed blood drawn for the initial matching and the fact that when the donor and recipient bloods were rechecked, both were found to be Type A and Rh+. Repeated attempts to demonstrate any subgroup Rh agglutinin\* in the recipient's blood were unsuccessful. These observations indicate that

the hemolytic reaction occurred before the patient received blood, presumably as a complication of the abortion.

Drugs capable of producing hemolysis that might have been employed include the sulfonamides, quinine and abortifacient pastes. No sulfonamide was found in the blood on admission. In view of the oliguria, which would have prevented appreciable excretion of sulfonamide and thus made detection possible, sulfonamide hemolysis was not likely.

The use of quinine as an oxytocic by illegal abortionists is an old practice, and it may have been used in this case. Cases of hemoglobinuria following

TABLE 1 Blood Data

TIME OF DETERMINATION	SPHEROCYTES per 100 red cells	SERUM HEMOGLOBIN mg/100 cc	SERUM BILIRUBIN mg/100 cc
On admission	15		2.08
After eight hours	8	222	1.48
After twenty hours	4	128	0.20
After eighty hours	2	54	0.90

quinine medication in patients without malaria have been reported.<sup>4-6</sup> The cases reported by Wakeman et al.<sup>5</sup> and by Terplan and Javert<sup>6</sup> also occurred in pregnant women who had been given quinine as an oxytocic. The case of Wakeman and his associates was so similar to the one reported above that the following summary is presented.

A 20-year old woman took quinine and ergot to induce an abortion. Three days later she noticed severe lumbar pain and began to vomit. She became jaundiced. On admission to the hospital the urine was dark, bloody red. The serum was very dark. Attempts to group the patient's blood showed that the serum agglutinated the cells of all donors. Severe oliguria developed and the nonprotein nitrogen rose to 237. Hemoglobin which was 73 per cent on admission fell to 43 per cent. Diuresis began on the ninth day and the patient recovered. Re-examination of the blood later failed to show the pan agglutination observed initially.

Severe intravascular hemolysis following the use of abortifacient pastes introduced into the uterus has been described,<sup>7</sup> the hemolysis being effected by the direct action of soft soaps on the red cells once they gain entrance to the blood stream.

Although the specific cause of hemolysis cannot be stated with certainty, the best explanation of the hemolytic reaction in this case seems to be either the introduction of an excess of a lytic substance into the blood stream by way of the uterus or sensitivity to orally ingested drugs.

### Physiological Changes following Hemolysis

The clinical and hematologic data and fluid balance in the case reported above are presented in Table 2. The severe uremia at the onset was undoubtedly due in large part to the liberation of nitrogenous material from the metabolized red cells, as in other types of hemolytic anemia.<sup>8</sup>

\*We are indebted to Dr. Louis K. Diamond for the Rh typing.



TABLE 2 Clinical and Hematologic Data

HOS- PAT. DAY	BLOOD UREA NITROGEN mg/100 cc	SERUM CHLORIDE m-equiv/liter	CARBON DIOXIDE m-equiv/liter	ALBUMIN gm/100 cc	GLOBULIN gm/100 cc	TOTAL PROTEIN gm/100 cc	PHOS- PHORUS mg/100 cc	CALCIUM mg/100 cc	HEMATO- CRIT vol %	WHITE CELL COUNT x 10 <sup>3</sup>	HEMO- GLOBIN gms/100 cc	INTRA- VENOUS cc	BLOOD cc	FLUID INTAKE PLASMA ALBU- MIN cc	ORAL cc	TOTAL cc	URINE cc	FLUID OUTPUT TOTAL cc	WEIGHT lb
1	170	110	15.2	3.0	3.0	6.0	—	—	10.0	41.9	222	1,000	400	—	—	1,400	30	30	61.9
2	177	116	17.8	3.0	3.0	6.0	—	—	15.0	38.5	128	1,150	500	—	—	3,230	18	300	—
3	242	101	26.4	2.6	2.6	5.0	—	—	16.0	17.6	80	2,150	500	200	—	2,130	156	180	—
4	176	99	25.4	2.8	2.0	4.8	—	—	15.2	23.1	54	2,000	500	—	—	3,350	117	350	59.1
5	185	92	25.0	2.8	2.0	4.8	—	—	20.2	23.1	18	2,000	500	—	—	3,350	42	350	59.3
6	220	91	23.6	2.7	2.0	4.7	—	—	22.0	—	—	2,000	500	600	—	3,350	273	200	61.3
7	218	88	26.0	—	—	5.0	6.7	—	20.5	17.5	—	200	—	200	—	750	47	280	61.2
8	—	—	—	—	—	—	—	—	20.5	—	—	—	—	250	795	1,045	58	100	61.2
9	266	88	19.6	3.2	2.5	5.7	—	—	20.2	—	—	1,290	—	250	—	1,540	110	265	61.2
10	257	89	18.8	—	—	6.1	—	—	—	—	—	1,150	—	250	—	1,400	625	955	61.2
11	—	—	—	—	—	—	—	—	—	—	—	1,400	—	—	—	1,150	330	955	61.2
12	256	90	21.0	—	—	—	3.8	3.9	—	—	—	2,000	—	500	125	2,225	520	970	61.0
13	—	—	—	—	—	—	—	—	—	—	—	2,000	—	500	130	2,180	985	270	61.3
14	266	85	20.1	—	—	—	—	—	—	—	—	2,000	—	300	26	2,176	1,170	550	61.2
15	—	—	—	—	—	—	—	—	20.2	—	—	4,000	—	300	88	4,388	1,115	820	61.2
16	216	85	20.0	2.7	3.6	6.3	—	—	—	—	—	2,200	—	300	—	2,500	2,445	595	61.3
17	—	—	—	—	—	—	—	—	—	—	—	2,200	—	—	—	2,500	2,415	330	61.8
18	174	76	20.3	—	—	—	—	—	—	—	—	1,550	—	200	—	1,750	2,625	335	61.8
19	197	93	20.0	—	—	—	—	—	—	—	—	3,000	—	—	—	4,720	1,600	210	59.0
20	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	2,850	2,650	200	57.6
21	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,650	2,650	—	57.6
22	131	96	18.6	—	—	—	—	—	—	—	—	2,000	—	—	—	1,875	4,310	60	54.0
23	—	—	—	—	—	—	—	—	16.0	10.2	—	2,000	—	—	—	1,730	2,610	200	53.6
24	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,915	2,610	180	53.8
25	110	102	15.6	4.2	3.0	7.2	1.9	4.2	18.6	11.0	—	2,000	500	—	1,710	2,230	2,260	180	53.8
26	—	—	—	—	—	—	—	—	—	13.7	—	2,000	—	—	—	1,810	2,260	300	53.4
27	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,810	3,000	350	53.4
28	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	1,215	1,655	100	53.4
29	—	—	—	—	—	—	—	—	—	—	—	2,000	—	—	—	2,810	2,950	—	53.2
30	108	107	13.8	—	—	6.8	1.6	3.6	—	—	—	—	—	—	—	2,770	2,770	—	53.2
31	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,230	2,250	—	52.6
32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,500	2,420	—	52.6
33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,500	3,440	—	53.0
34	79	109	15.6	4.2	3.3	7.5	1.3	4.8	13.5	—	—	—	—	—	—	3,110	2,950	3,440	52.4
35	—	—	—	—	—	—	—	—	19.8	—	—	—	500	—	—	3,250	3,150	3,150	52.0
36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,210	3,100	3,100	52.2
37	81	101	12.9	—	—	—	—	—	—	6.2	—	—	—	—	—	4,410	3,350	3,350	51.6
38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,200	3,130	—	51.6
39	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,000	3,350	—	51.0
40	63	110	—	—	—	—	—	—	—	7.6	—	—	—	—	—	3,950	3,100	3,350	51.0
41	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,850	3,150	350	50.7
42	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,750	3,840	—	50.7
43	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,950	3,350	—	50.1
44	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,950	3,800	—	50.1
45	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,550	2,950	—	49.9
46	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,550	3,600	—	49.9
47	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,280	3,550	—	49.9
48	38	110	17.7	—	—	—	—	—	21.5	8.2	—	—	—	—	—	4,510	3,550	—	49.2
49	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,900	2,550	—	49.2
50	—	—	—	—	—	—	—	—	—	—	—	1,000	—	—	—	3,340	4,350	—	49.6
51	29	105	18.4	—	—	—	—	—	—	—	—	—	—	—	—	3,950	4,660	—	49.6
52	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,710	3,200	—	49.8
53	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,500	3,660	—	49.8
54	14	111	17.9	—	—	—	—	—	20.0	—	—	1,000	—	—	—	3,740	4,040	—	50.1
55	—	—	—	—	—	—	—	—	—	—	—	1,200	—	—	—	4,200	4,140	—	50.1
56	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,240	3,500	—	49.1
57	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,000	3,150	—	49.1
58	17	112	20.0	—	—	—	—	—	19.0	—	—	—	—	—	—	3,610	4,200	—	49.8
59	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,870	2,750	—	49.8
60	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,910	3,350	—	50.6
61	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	4,500	4,350	—	50.6
62	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,440	2,740	—	50.2
63	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,300	—	50.2
64	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	3,300	—	50.0
65	26	109	21.6	4.2	3.2	7.4	—	—	—	—	—	—	—	—	—	3,000	2,600	—	50.4
66	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	2,600	—	50.4
67	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	3,000	2,600	—	50.4
68	28	107	—	—	—	—	—	—	—	—	—	—	—	—	—	4,450	3,350	—	51.0

\*Estimated.

Oliguria, amounting almost to anuria, extended over a period of twelve days, and persistent vomiting during that period not only made feeding by mouth impossible but also caused considerable loss of electrolytes. Therapy was aimed at replacement of water, salt, plasma protein and erythrocyte deficits. Glucose and plasma served to satisfy metabolic needs in part and to prevent excessive tissue catabolism. Greater restriction of fluid was necessary at the end of the first week with the

day. Pyuria also persisted until that time. The specific gravity was fixed during the first hospital admission at 1.010. On readmission a causal specimen showed a specific gravity of 1.018. These observations are all consistent with the pathological localization of the renal lesions primarily in the convoluted tubules, with subsequent repair.

It is interesting to observe that hematopoiesis was depressed during the period of convalescence so long as the blood urea nitrogen was elevated, and

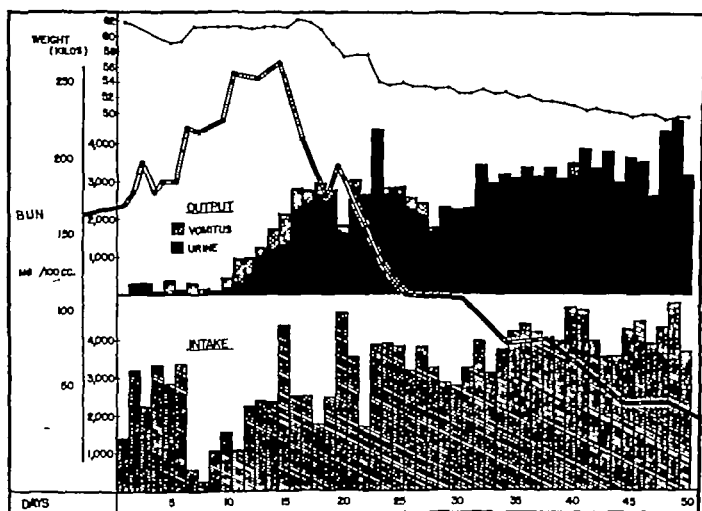


FIGURE 4 Chart Depicting the Fluid Balance of the Patient during the Period of Anuria and Recovery

development of edema and hydrothorax. No determinations of serum potassium were made, but electrocardiographic changes consistent with high potassium levels<sup>9</sup> were not found.

With the onset of diuresis on the tenth day, the maintenance of fluid and electrolyte balance became easier. Renal function was so impaired at that time, however, that the blood urea nitrogen continued to rise (Fig 4). Urea clearance over the following weeks improved (Fig 2), and normal blood values were reached on the fifty-fourth day. Phenolsulfonophthalein excretion was likewise negligible at first. Inability of the tubular cells to reabsorb salt was demonstrated by a progressive fall in the blood chloride to 76 milliequiv per liter on the eighteenth day. Subsequently, it was necessary to provide from 3 to 12 gm of salt daily to keep the patient in salt balance. Proteinuria—as much as 8 gm was excreted on the fifteenth day—gradually diminished, disappearing on the forty-fifth

indeed for several weeks afterward. This patient was studied by the injection of radioactive iron intravenously and showed, as all uremic patients do, a decreased utilization of iron for hemoglobin formation.<sup>10</sup> When the azotemia had disappeared, however, active erythropoiesis was resumed, and a deficit of approximately 900 cc of red cells was made up in a little more than a month.

#### HEMOGLOBINURIC NEPHROSIS

##### Occurrence

The majority of reported cases of hemoglobinuric nephrosis have occurred after transfusion reactions due to incompatibility between major blood groups or to Rh incompatibility.

Hemoglobinuric nephrosis also follows blackwater fever,<sup>11-13</sup> favism,<sup>11-17</sup> hemolytic reactions due to sulfonamides,<sup>18-20</sup> plasmoquine<sup>21</sup> and quinine<sup>22</sup> intoxication, arsine poisoning<sup>23</sup> and hemolytic reac-

tions following burns<sup>28</sup> and the intravenous injection of distilled water<sup>29</sup>

Hemoglobinuric nephrosis is rare or has not been reported in certain other hemolytic syndromes — namely, paroxysmal cold hemoglobinuria, paroxysmal nocturnal hemoglobinuria, cold hemoglobinuria due to a high titer of cold agglutinins and hemolysis of the recipient's cells due to a high titer of isoagglutinins in Group O blood from a universal donor

### *Renal Pathology\**

The pathological changes in the kidneys following intravascular hemolysis are described by a number of authors,<sup>30-32</sup> but the most complete description of the sequence of events is given by Ayer and Gauld.<sup>33</sup> These writers describe the autopsy findings in 7 patients who died three hours to ten days after hemolytic reaction

Three hours after hemolysis there was glomerular swelling, slight cloudy swelling of the proximal convoluted tubules and pale acidophilic material in the lumens of the proximal tubules, which became dark red to brown in the distal convoluted and collecting tubules. No interstitial edema or leukocytic infiltration was noted

By the third day there was considerable brick-red pigment within the cells of the distal convoluted tubules and some sloughing of these cells. The glomeruli and the proximal convoluted tubules were normal in appearance. By the sixth day there was considerable interstitial edema and leukocytic infiltration around the convoluted tubules. There was marked desquamation of the tubular cells, and some of the pigment of the lumens was turning greenish yellow. By the seventh day a few mitotic figures appeared in some of the tubular cells, indicating attempts at repair. Destruction of tubular cells and interstitial infiltration and edema were still more pronounced

By the tenth day there was complete destruction of some tubules, which were replaced by inflammatory cells and fibroblasts. There were numerous cellular casts in the distal convoluted and collecting tubules. Practically all the inflammation was around the distal convoluted tubules. There is little information available regarding what happens after the tenth day in cases that go on to recovery. Except for a case in which the patient recovered from a transfusion reaction and died fourteen months later of a pre-existing chronic glomerulonephritis, no autopsy reports of patients who had recovered from a hemoglobinuric nephrosis could be found

The changes found in the kidneys in the case presented above were consistent with the healed stage of the pathologic sequence described. The

pattern of scarring suggests that single nephrons or groups of nephrons had been destroyed. Added support to this thesis is the fact that few glomeruli and no blood vessels were involved, and none of the changes were those that are seen in the usual types of kidney disease

Pathological descriptions of the renal lesions in other varieties of hemoglobinuria<sup>6, 20, 34</sup> are identical to those mentioned above after incompatible transfusion reactions

### *Pathogenesis*

In early pathological studies, emphasis was placed on the capacity of heme pigments to block renal tubules. Animal observations showed a much greater tendency for hemoglobin precipitation in acid urine<sup>35</sup>; accordingly, it was assumed that renal damage was directly related to hemoglobin precipitation, which in turn was related to urinary acidity

There are noticeable exceptions to this explanation.<sup>11, 33</sup> Both experimentally and clinically, it has been noted that hemoglobinuria in the presence of an acid urine does not always result in oliguria and, conversely, that preliminary alkalization does not always protect against severe or fatal renal damage. Fatal cases have been reported in which there has been too little renal precipitation of hemoglobin in the pathological sections<sup>36</sup> to account for anuria. Foy et al.,<sup>11</sup> in an excellent review on this subject, concluded that precipitation of hemoglobin is secondary to the oliguria and not the cause of it

Apparently, a number of factors may operate to produce renal damage, and prominent among these is shock, regardless of the cause. Whether from hemolytic anemia, toxins, infections or trauma, the renal changes are strikingly similar.<sup>37</sup> The resulting tubular necrosis is considered to be due to anoxia from the critically reduced renal blood flow. The presence of hemolysis has been shown to cause further reduction of renal blood flow through local vascular spasm.<sup>38</sup> Finally, Yuile<sup>39</sup> has demonstrated quite clearly that tubular necrosis due to anoxia results in extensive hemoglobin precipitation in the tubules of experimental animals

Dehydration and electrolyte imbalance contribute to circulatory failure. Vomiting may be severe with the sudden azotemia and, in the absence of renal regulation, may increase electrolyte loss, which in itself can perpetuate renal dysfunction.<sup>11</sup>

The careful observations of Bing<sup>40</sup> indicate a difference in toxicity of certain products of hemoglobin. Methemoglobin appeared much more toxic in acidotic dogs than bivalent hemoglobin. Formation of methemoglobin in blood serum is dependent on the length of time the hemoglobin is circulating in the serum and on the reducing capacity of the serum, in the urine, methemoglobin formation is greater in acid mediums. The possibility that other hemoglobin derivatives such as hematin cause local renal injury is suggested

\*After this article was submitted an excellent study of the pathology of hemoglobinuric nephrosis and related conditions was published by Lucké (Lucké B. Lower nephron nephrosis: renal lesions of crush syndrome, of burns, transfusions and other conditions affecting lower segments of nephrons. *Mil Surgeon* 99:371-396, 1946)

As Foy et al.<sup>11</sup> point out, most of the experimental studies on hemoglobinuric nephrosis have been carried out with the observer's attention concentrated on one factor. It seems fairly evident that no one factor is solely responsible for the renal change, and further studies in which each of the various factors is carefully controlled are necessary for a complete understanding of the pathogenesis.

#### Prognosis

The mortality rate for hemoglobinuric nephrosis cannot be accurately calculated from the published

the case reported above are shown in Figure 2. The rate of recovery was slow, but the degree of recovery was fairly complete. The final phenol-sulfonephthalein determination was probably deceptively high, owing to the impairment of liver function existing at the time, but the curve shows progressive improvement until the time of death. The urea clearance apparently remained stationary at about 30 per cent between the seventieth and ninetieth days.

The prognosis of this renal lesion has much in common with other types of tubular damage, such

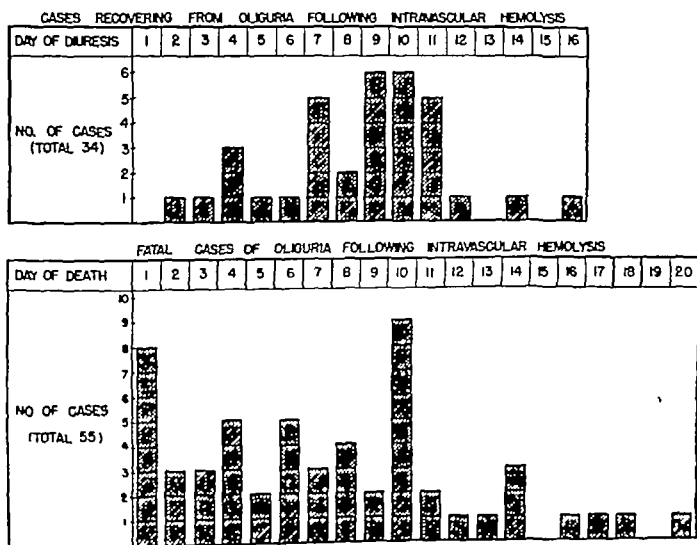


FIGURE 5 Day of Diuresis or Day of Death in the Cases of Oliguria following Intravascular Hemolysis Reviewed in the Literature

cases, since a greater proportion of fatal than nonfatal cases have undoubtedly been reported. Fifty-five fatal and 34 nonfatal cases of hemoglobinuric nephrosis collected from the literature are presented in Figure 5 according to date of death or onset of diuresis. It is apparent that the critical period following the hemolytic reaction lasts approximately two weeks. If the patient can be kept alive through that period, the kidneys may be expected to resume adequate function.

In only 7 of the 34 nonfatal cases were renal-function tests performed after clinical recovery. In all these cases function was normal, or nearly so. No case was encountered in the literature in which renal damage due to hemoglobinuria persisted for as long as a year. The results of the renal-function tests in

as bichloride of mercury poisoning and shock states. Except for the initial accelerated rise of the non-protein nitrogen with blood destruction, each case goes through the same critical period, repair proceeds at the same rate, and functional recovery is practically complete.

#### Therapy

Treatment may be divided into the periods of hemoglobinemia, anuria and diuresis.

In the acute reaction with hemoglobinuria immediate attention should be directed to the prevention of shock and the promotion of renal blood flow. Transfusion is indicated, particularly in the presence of anemia. Plasma in amounts up to 1 or 2 liters a day or even physiologic saline and

glucose solutions are useful. Amounts of crystalloids in excess of 2 or 3 liters a day, however, are to be guarded against, because of the danger of edema if anuria develops. Immediate alkalization is indicated in spite of the conflicting experimental evidence regarding its effects. This may be done by the injection of 6 gm of sodium citrate, lactate or bicarbonate intravenously over a period of five or ten minutes.<sup>41</sup> The large doses of potassium sometimes advocated for alkalization are not without danger,<sup>9</sup> particularly in view of the large amount of potassium already liberated by the hemolytic reaction.

After the first one to four days, the hemoglobinemia will have disappeared, and renal shutdown taken place. As indicated above, the lesion is reversible, given sufficient time for repair. The important factor, therefore, once anuria has set in, is time, and the maintenance of the patient depends on the prevention of edema and congestive failure, maintenance of blood volume and renal blood flow, maintenance of electrolyte balance and provision of basal nutrition requirements.

The anuric patient differs from other patients in an important respect: water and not salt is the important factor in edema formation. Without renal excretion there is a relatively fixed daily fluid output through other channels. If the fluid intake exceeds this, edema follows, regardless of the electrolyte situation. Fluid retention, in addition to causing congestive heart failure, produces functional impairment of other vital organs, particularly the brain, with cerebral edema, convulsions, coma and death. With its volume limited by a fibrous capsule, the kidney parenchyma is likewise affected by edema.

Fluids should be limited to about 1500 cc a day, subject to modification according to the cardiac reserve and evidence of congestive failure. Blood and plasma are useful in maintaining the blood volume. Electrolyte supplements are necessary to replace those lost from the body by vomiting and diarrhea. These are prescribed according to daily determinations of the total protein, chloride and carbon dioxide combining power. Prophylactic digitalization is indicated to prevent congestive failure. Should cardiac function be impaired at the onset, it may be anticipated that the patient will not survive the critical period of one or two weeks. Under such circumstances, peritoneal irrigation may be life saving. It has been demonstrated that the peritoneal surface serves as an adequate excretory organ (by diffusion) if irrigated with the proper solution.<sup>42</sup> Renal decapsulation has been reported to produce dramatic results in a few cases, and it affords an opportunity for renal biopsy. It is directed, however, at prevention of the harmful effects of renal edema, which may at least in part be controlled by limited fluid administration.

Although the urine volume may become greater than normal shortly after the onset of diuresis, the nonprotein nitrogen may continue to rise. The urine at that time is almost a pure plasma filtrate—instead of the glomeruli putting out 170 liters of fluid a day and the tubules absorbing 99 per cent of the fluid, the kidney excretes 2 or 3 liters of what is approximately plasma, partially filtered of protein. This lack of tubular activity is shown as the diuresis progresses, by an inordinate loss of sodium chloride, which in itself may cause severe renal dysfunction unless corrected.<sup>43</sup> It is conceivable that other elements usually reabsorbed escape into the urine in excess—that is, glucose, calcium and potassium—and in themselves cause deficiency syndromes.

The period of tubular repair following the onset of diuresis may last from several weeks to several months. During this period of repair, fluids should be forced, and the intake of salt kept high (between 6 and 12 gm daily) to compensate for the salt-losing tendency that persists until the tubular damage is repaired.

#### SUMMARY

The pathogenesis of hemoglobinuric nephrosis is discussed, and suggestions regarding therapy are made.

A case of hemoglobinuric nephrosis following massive intravascular hemolysis is presented. The patient recovered but died three months later of an acute hepatic necrosis due to homologous serum hepatitis.

Renal-function tests improved until the time of death, indicating eventual complete recovery, and autopsy showed little residual kidney damage.

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## GRANULOMA INGUINALE WITH PERIANAL INVOLVEMENT

### Report of a Case

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GRANULOMA inguinale is an unusual skin disease found preponderantly in Negroes. The lesion begins as an ulceration in the groin or about the genitals and over a period of years, if untreated, spreads locally and progresses to a chronic inflammatory granulomatous stage. A gram-negative encapsulated bacillus appearing as a rod-like structure (Donovan body) in large mononuclear cells is the etiologic organism.<sup>1,2</sup>

Involvement about the anus is rare, and yet within the past year 2 cases with perianal disease have been described in Negro soldiers stationed at a camp in Massachusetts.<sup>3</sup> In the ulcerative stage the chief complaints are pain and perianal drainage. The pain is constant and annoying on sitting and on walking but is agonizing on defecation, especially if the anal canal is involved. Drainage is bloody, serous or purulent, resulting in redness and irritation of the perianal skin. With progress of the disease and granuloma formation the pain tends to diminish in intensity, and the drainage becomes more profuse and foul smelling. Specific treatment consists of two courses of intramuscular antimony (Fusidin).

Inasmuch as granuloma inguinale is found primarily in warm climates and particularly in Negroes, the following case in a white man is considered worthy of report.

A 29-year-old man was seen in consultation on July 5, 1946, because of a painful draining perianal mass of 9 months duration. He had been born in the northeast section of Massachusetts and except for a short period in the military service, had spent his entire life there. While in the service he had been stationed at various camps in Massachusetts, Florida and Texas. In August, 1945, he had been separated from the service because of poor vision. In September he had first noticed a small tender swelling just to the left of the anus associated with severe pain on defecation. The bowel movements at that time were scybulous and there was occasional bright-red staining on the toilet tissue. A physician informed him that he had a "pimple" 1 cm from the anus and prescribed a dark salve for local application and also warm water poultices. Within a few days the mass broke down, and purulent drainage ensued. During the next few months there was intermittent crusting and recurrent drainage. The pain became intolerable and was controlled by narcotics. In April, 1946, the patient was seen by another physician who advised admission for observation to a hospital where physical examination disclosed a well developed and well nourished man who stood with the feet apart and who was bent forward for relief of pain. The right side of the anal canal contained a large area of ulceration extending down to the scrotum that bled easily after the overlying purulent discharge and debris had been removed and on which pink granulations were noted. On the left side a smaller area about 5 cm in diameter, was noted. The sphincter was intact and painful to examination. There was

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no evidence of hemorrhoids or fistulas. On April 29 the pathological report on a biopsy specimen taken 2 days previously revealed marked chronic inflammation and epithelial hyperplasia, early carcinoma could not be ruled out. On May 10 section of the left inguinal lymph node showed essentially normal lymphoid tissue, and the capsule disclosed slight round-cell infiltration. On May 25 biopsy of the rectum revealed marked acute and chronic inflammation compatible with lymphogranuloma inguinale. A Frei test was suggested. On May 28 it was stated that the picture was one of chronic and acute inflammation, of nonspecific type, there was no evidence of cancer. After 41 days of hospitalization, the treatment consisting of wet dressings and 6,360,000 units of penicillin, the patient was discharged unimproved, in agonizing pain — especially on defecation — and draining a profuse amount of foul pus from the perianal lesion.

The past history was entirely negative for serious sickness or operations. There was no history of contact with Negroes or of any unprotected contact.

Physical examination disclosed a young man lacking in education and of low intelligence who was poorly nourished and in obvious acute distress. Except for the perianal region,

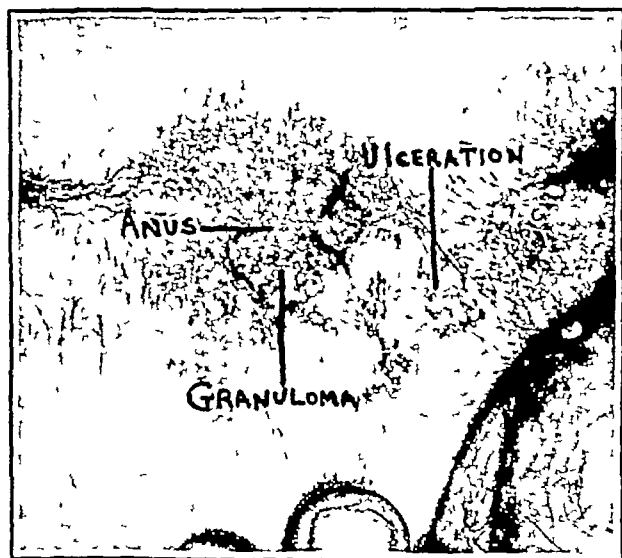


FIGURE 1 Photograph of the Active Lesion

The lesion on the anterior and left lateral aspects of the anus is ulcerated, granulomatous and covered with pink, easily bleeding granulations.

the skin was clear. The pupils reacted equally to light and to accommodation. There was no adenopathy. The heart sounds were of good quality, with normal rate and rhythm. The chest expanded symmetrically, numerous crackling rales were heard over both bases, clearing after cough. Abdominal examination was negative. There was a healed scar over the left inguinal region. The genitalia were normal. The reflexes were equal and active. About the anus anteriorly and especially on the left side there was an elliptical lesion approximately 7 cm in length and 1 cm in width, ulcerated anteriorly and granulomatous along the left side (Fig. 1). The mass was covered with pink granulations, which bled easily on trauma. The slightest pressure resulted in such excruciating pain that further examination was deferred. A diagnosis of probable granuloma inguinale was made, and hospitalization arranged for the following day.

The temperature was 98.6°F, the pulse 96, and the respirations 20.

Examination of the blood revealed a red-cell count of 4,910,000, with a hemoglobin of 96 per cent, and a white-cell count of 12,600, with 57 per cent neutrophils, 18 per cent band cells, 19 per cent lymphocytes and 6 per cent monocytes. The bleeding time was 3 minutes (Duke), and the clotting

time 5 minutes (capillary tube), and the sedimentation rate 10 mm in 1 hour (Wintrobe method). The Frei test and the blood Hinton test were negative 72 hours after admission. The urine was straw colored, cloudy and alkaline, with a specific gravity of 1.016, tests for albumin and sugar were



FIGURE 2 Photomicrograph of the Biopsy Specimen (x100)

Note the marked chronic inflammation in the subpapillary connective tissue.

negative. Microscopical examination of the sediment was negative for red cells and casts.

Strict bed rest was enforced and Furacin-ointment dressings applied to the perianal region, 0.06 gm of codeine sulfate

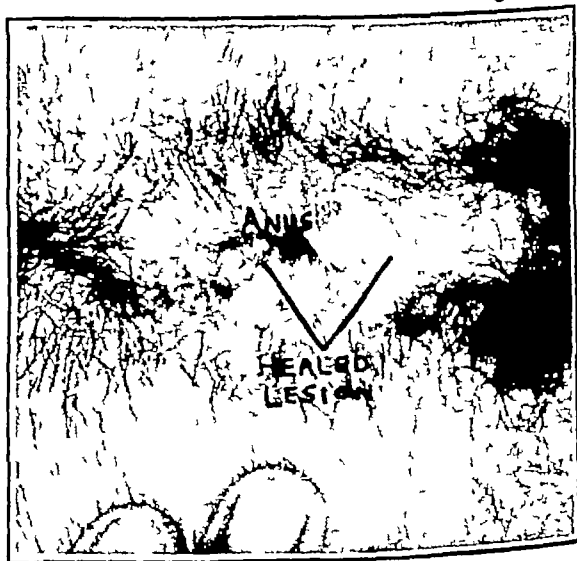


FIGURE 3 Photograph of the Healed Lesion

The perianal lesion is healed after fourteen days of specific treatment.

and 0.6 gm of aspirin were administered for relief of the pain. Intragluteal injections of Fuadin (sodium antimony-III biscatechol disulfonate of sodium) were instituted on the day of admission, alternating buttocks being used, and a complete course (40 cc) given according to the following schedule on

July 6, 7, 8 and 10 respectively, 1.5, 3.0, 5.0 and 5.0 cc., followed by 5.0 cc. every other day until the full amount had been given. Biopsy specimens and smears were taken from the perianal lesion on July 9. The smear was negative for acid fast bacilli and for inclusion bodies. Microscopical examination of one biopsy specimen revealed a thickening of the epidermis, with edema, polymorphonuclear-cell and lymphoid cell infiltration of the papillae and a dense lymphoid and plasma-cell exudate in the subpapillary connective tissue. There was no evidence of tuberculosis, and the inflammatory process was considered nonspecific. The diagnosis was chronic and acute inflammation. Microscopical examination of the other specimen disclosed marked chronic inflammation and epithelial hyperplasia compatible with granuloma inguinale (Fig. 2).

On the 4th hospital day there was little drainage and the pain had diminished noticeably. At that time the ulcerated portion of the lesion showed evidence of crusting and drying and there was a definite decrease in redness about the entire area. Clinical improvement was marked and the patient was allowed out of bed. During the following week the ulceration gradually healed and the granuloma was absorbed. All symptoms subsided. The first course of treatment was completed on July 20, and 2 days later the patient was discharged to his own physician for the second course, with the lesion apparently healed (Fig. 3). Despite the fact that this course was never completed, owing to indifference on the part of the patient there has as yet been no recurrence.

Several aspects of this case are worthy of consideration. The diagnosis of granuloma inguinale is extremely difficult, not only because the lesion is not suspected but also because smears and biopsy

specimens often do not reveal the diagnostic bacteriologic and pathological findings. The disease should be suspected in every ulceration or granuloma of the anogenital region that is resistant to antibiotics and to chemotherapy. Even though the characteristic macrophage with intracellular Donovan bodies is not found on smear examination and the pathological picture is that of acute or chronic inflammation or of nonspecific granuloma, a therapeutic trial of intramuscular antimony (Fuadin) should be instituted.

Granuloma inguinale can become a chronic disabling disease, if not recognized. Clinical response to Fuadin is usually prompt, dramatic and specific. The case reported is of interest in that it occurred about the anus and in a white man living in Massachusetts.

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## MEDICAL PROGRESS

### "FOLIC ACID" PTEROYLGLUTAMIC ACID AND RELATED SUBSTANCES\*

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#### DISCOVERY, SYNTHESIS AND CHEMISTRY

THE discovery, isolation, synthesis and clinical use of a new member of the vitamin B complex called "pteroylglutamic acid" can be attributed to the combined efforts of many different investigative groups. During the past sixteen years this substance has ascended from bacteria to chick, from chick to rat, from rat to monkey and from monkey to man as an essential nutrient. During its ascent, but before its isolation and synthesis, this substance picked up many names (Table I), for each group of investigators that studied it did not then realize that their material was quite similar to that described by others. This varied nomenclature was the natural consequence of preliminary work on an unknown substance, but the identity of this nutritive essential was clarified when it was shown that the factor in liver essential for the growth of *Lactobacillus casei* was also necessary for chicks, rats, monkeys and man.

Various investigative groups have demonstrated that in such foods as yeast, liver and spinach, there is a substance or group of substances that is closely associated with known members of the vitamin B complex and is necessary for the growth and hematopoiesis in the chick, the rat and the monkey, as well as for the growth of certain bacteria. Investigators working chiefly with yeast isolated a material known as the *L. casei* factor because it was necessary for the growth of that organism.<sup>2-4</sup> From liver a substance was isolated that prevented the development of anemia, leukopenia and thrombocytopenia and restored growth in the chick.<sup>4</sup> This substance was called vitamin B<sub>12</sub>. From both liver and yeast a factor was isolated that prevented the development of cytopenia and a sprue-like syndrome in monkeys fed a synthetic diet containing all previously known essential nutrients.<sup>2-4</sup> This factor was named vitamin M. As knowledge of these apparently different factors accumulated, it occurred

\*Based on a talk presented at a meeting of the Begg Society of Boston University School of Medicine, Boston, on April 7, 1947.

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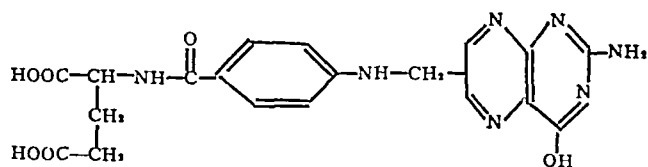
to various investigators that they might be dealing with the same substance. It was rapidly shown that the *L. casei* factor could replace vitamin B<sub>12</sub> in chick nutrition and could correct the sprue-like syndrome in monkeys deficient in vitamin M.<sup>2-4</sup> Furthermore, it was found that the *L. casei* factor corrected the anemia, leukopenia and granulocytopenia and restored growth to rats fed sulfonamides.<sup>2-5</sup> When it had been demonstrated that these various factors

TABLE 1 Early Names Applied to "Folic Acid"\* by Various Groups of Investigators

SUBJECT OF BIOLOGIC ACTIVITY	NAME
Bacteria	
<i>Lactobacillus casei</i>	<i>L. casei</i> factor, norite eluate factor, yeast factor, fermentation factor
<i>Streptococcus lactis R</i> ( <i>Str. faecalis</i> )	<i>S. lactis R</i> factor, folic acid*
Chick	Vitamin B <sub>12</sub> , vitamin B <sub>12</sub> conjugate, vitamin B <sub>12</sub> , vitamin B <sub>12</sub> , factor U, factor R, factor S
Monkey	Vitamin M
Man	Wills factor (?)

\*Folic acid was the name given by Mitchell and his associates<sup>1</sup> to a factor extracted from spinach essential for the growth of *S. lactis R*. This substance is not identical with the *L. casei* factor but has been extracted from liver, kidney, yeast and mushrooms. "Folic acid" has come into popular usage as the descriptive term for pteroylglutamic acid and its related substances. Throughout this paper these substances are designated by their accepted chemical names when the names are known.

were probably closely related, if not identical, the *L. casei* factor was crystallized from a liver concentrate, its chemical structure determined, and its synthesis achieved.<sup>2-4, 6</sup> The active nutrient thus isolated proved to be a relatively simple organic compound containing the amino acid, glutamic acid, para-aminobenzoic acid and the pterin nucleus related to xanthopterin, the chemical that gives the yellow color to the butterfly wings. These various fractions of the active material are combined as follows:



This compound is called pteroylglutamic acid. It is the active substance in the preparations formerly called vitamin B<sub>12</sub>, vitamin M and *L. casei* factor. "Folic acid" is the term that, by popular usage, has become synonymous with pteroylglutamic acid, but throughout this review the latter chemical name is used. Pteroylglutamic acid is a bright-yellow material that is only slightly soluble in water. Its sodium salt is more soluble. Sunlight has a destructive action on a solution of pteroylglutamic acid, and this compound is rapidly destroyed by heating with dilute mineral acids.<sup>7</sup>

A series of compounds containing more than one glutamic acid molecule has been isolated from various sources. The active material in the preparation containing the so-called "fermentation *L. casei* factor" has recently been identified and synthesized. This factor occurs in a concentrate of the filtrate obtained from the products of aerobic fermentation of an unidentified bacterium of the genus *Corynebacterium*.<sup>8</sup> The active material possesses two extra glutamic acid molecules bound through a peptide linkage to pteroylglutamic acid. This compound is known as pteroyltriglutamic acid (or pteroyldiglutamyl-glutamic acid). A different chemical was isolated from a yeast concentrate. This compound, formerly known as vitamin B<sub>12</sub> conjugate, proved to have six molecules of glutamic acid combined—probably through a peptide linkage—to pteroylglutamic acid. Hence, it was named pteroylheptaglutamic acid (or pteroyl-hexaglutamyl-glutamic acid). The exact structure of this compound is not known, for it has not been synthesized. In the literature pteroylheptaglutamic acid is frequently referred to as "folic acid conjugate." Recently, a compound containing thirteen glutamic acid molecules has been isolated from yeast.<sup>9</sup> The exact chemical structure has not been determined. On the basis of these chemical studies it seems reasonable to infer, as Thomson<sup>9</sup> has implied, that a whole series of compounds that might collectively be called the pteroylpolyglutamic acids exists in nature.

Pteric acid is a synthetic compound containing no glutamic acid molecules.<sup>6</sup> This compound has relatively limited biologic activity.

#### ASSAY AND NATURAL DISTRIBUTION

The amount of pteroylglutamic acid or its related conjugates in foods and biologic fluids can now be determined only by bioassay, the growth of *L. casei* or *S. lactis R* being used as the test organisms. The amount of growth of these bacteria in a given time is estimated turbidimetrically. From a standard curve the concentration of active material in the unknown substance can be estimated. This assay, to be accurate, depends on knowledge of the nutritional requirements of these test organisms. Table 2 presents the relative biologic activity of pteroylglutamic acid and related substances for *S. lactis R* and *L. casei*. Two points should be emphasized: the nutritional requirements of the test bacteria are different regarding their need for these growth-promoting factors and compounds containing more than one glutamic acid molecule are less active than pteroylglutamic acid in promoting growth.

It is the second point that is especially important in the assay of pteroylglutamic acid in foods, for in nature this nutrient almost uniformly occurs as pteroylheptaglutamic acid.<sup>10</sup> Because this heptapeptide is relatively impotent as a growth-promoting factor, the compound must be hydrolyzed into simple

pteroylglutamic acid, which is a potent growth factor. This hydrolysis may be achieved in a number of ways. Some investigators employ the enzyme takadiastase, other workers use an alkaline or acid hydrolysis. In animal tissues an enzyme has been found that hydrolyzes pteroylheptaglutamic acid into pteroylglutamic acid and six molecules of glutamic acid.<sup>11, 12</sup> This enzyme is designated vitamin B<sub>9</sub> conjugase because it splits the heptapeptide vitamin B<sub>9</sub> conjugate (pteroylheptaglutamic acid). Vitamin B<sub>9</sub> conjugase has been found in relatively abundant amounts in the liver, kidneys, bone marrow and pancreas. In the microbiologic assay for pteroylglutamic acid a water extract of fresh hog kidney is used as a source of vitamin B<sub>9</sub> conjugase.<sup>10</sup> There is, however, a limitation to this method — namely, the occurrence in food of a substance called "conjugase inhibitor."<sup>10</sup> Because this factor, which inhibits the activity of vitamin B<sub>9</sub> conjugase, occurs in variable amounts in food and because there is at

studied. Furthermore, the optimal daily allowance of this nutrient for human beings has not been determined.

### PHYSIOLOGY

The reported signs of pteroylglutamic acid deficiency are summarized in Table 4. It is apparent that a wide variety of signs are associated with a

TABLE 3 Content of Pteroylglutamic Acid in Various Foods<sup>10, 13</sup>

Food	PTEROYLGLUTAMIC ACID CONTENT microgram./100 gm.
Fresh deep green leafy vegetables	80-190
Liver	48-105
Fresh green vegetables; cauliflower	40-62
Kidney	35-47
Dry breakfast cereal prepared from wheat	19-46
Beef; veal	11-22
Root vegetables, tomatoes, cucumbers, light green leafy vegetables, bananas, pork, ham, lamb, cheese, milk, dry breakfast cereal prepared from rice or corn and many canned foods	0-20

TABLE 2 Relative Biologic Activity of Pteroylglutamic Acid and Related Substances<sup>1</sup>

SUBSTANCE	ACTIVITY		
	<i>S. lactis</i>	<i>R.</i>	<i>L. casei</i>
Pteric acid	50.0	0	0.01
Pteroylglutamic acid	100.0	100.0	0
Pteroylhistidylglutamic acid	7.5	8.0	0
Pteroyllysylglutamic acid	0.3	0	2

deficiency of this substance. Of special interest, however, are the hematopoietic disturbances in various animals and the syndrome similar to cytopenia and sprue that occurs in monkeys. The hematopoietic disturbances — anemia, leukopenia, granulocytopenia and thrombocytopenia — that occur in the lower animals do so in animals maintained on a synthetic diet containing all the known nu-

present no way of destroying it, assays employing vitamin B<sub>9</sub> conjugase are necessarily of limited value. By the use of amounts of conjugase in excess of the inhibitor content of the particular preparation being assayed, this difficulty may in part be overcome. No matter which hydrolytic method is employed, however, the amount of pteroylglutamic acid found in various foods varies rather widely, and to date a completely satisfactory method of assay has not been worked out.

With these limitations in mind, some of the recent work on the concentration of pteroylglutamic acid in foods is presented in Table 3. A number of points should be emphasized. In the first place, even in foods containing relatively rich quantities of pteroylglutamic acid, the amount available is low. In the second place, cooking and storage at room temperature effect large losses of this nutrient.<sup>10, 12</sup> Finally, only small amounts of pteroylglutamic acid are present in the usual diet — amounts considerably less than that found therapeutically effective. The intestinal bacterial flora may contribute a large amount of this vitamin, for Williams and his associates<sup>14</sup> have shown that a wide variety of bacteria can synthesize folic acid and that the rat may obtain as much as 70 per cent of the daily intake of folic acid from bacterial activity. Biosynthesis of pteroylglutamic acid in human beings has not been

TABLE 4 Reported Signs of Pteroylglutamic Acid Deficiency\*

DEFICIENCY SIGN	TEST SUBJECT
Failure of growth	Chick, rat, guinea pig, mouse and monkey
Anemia	Chick, rat, monkey and man
Leukopenia	Rat, chick, monkey and man
Granulocytopenia	Rat, monkey and man
Thrombocytopenia	Chick and man
Poor feathering	Chick
Diarrhea	Monkey and man
Glaucosia	Monkey
Necrosis of gums	Monkey
Susceptibility to dysentery	Monkey
Acrometria	Monkey
Porphyria-like whistlers	Rat and chick
Subnormal hepatic level of pantothenic acid	Rat
Subnormal response to stilbestrol	Rat
Subnormal response to nicotin	Chick
Spastic type of cervical paralysis	Dog
Certain dermatologic syndromes	Turkey poult
Pterosis	Man
	Chick

\*Based on material presented by Daft.<sup>1</sup>

trients except pteroylglutamic acid. This factor specifically corrects all these disturbances when added to the purified diet.<sup>2, 15</sup>

In the syndrome similar to cytopenia and sprue that develops when monkeys are maintained on a purified diet, interest is great because of the homologous conditions in man — tropical and nontropical sprue and celiac disease. In fact, Jones, Warden and Darby<sup>16</sup> suggest that lack of vitamin M in the monkey is the experimental analogue of sprue in man. This deficiency syndrome in the monkey

consists of anemia, leukopenia, thrombocytopenia, gingivitis, necrosis of the gums, anorexia, diarrhea, susceptibility to dysentery (experimental or spontaneous infection) and finally death<sup>17, 18</sup> This syndrome, as well as sprue in man, responds to therapy with both pteroylglutamic acid and pteroyltriglutamic acid In addition to the steatorrheic diarrhea of man, certain cases of long-standing diarrhea among human beings have responded to treatment with pteroylglutamic acid<sup>19</sup> Coca<sup>20</sup> reported that 6 patients with the dermatologic syndrome, who presented symptoms and signs that did not respond to routine therapy for allergy, were successfully treated with pteroylglutamic acid These patients had nervous symptoms or dermatologic disturbances, or both The former included "anorexia, weakness, uncontrollable nervousness and insomnia," and the latter either "chronic early inflammatory eruptions of both legs" or "widespread weeping eruption of limbs, body and face"

Because there is little fundamental knowledge concerning the mode of action of pteroylglutamic acid, few broad hypotheses have been suggested Two theories should be mentioned On the one hand it has been suggested that pteroylglutamic acid acts as a co-enzyme in the synthesis of thymine (5-methyl uracil—a pyrimidine not to be confused with thiamine) or a related compound<sup>15</sup> The evidence for this mode of action, however, is far from convincing By analogy, it is reasonable to suspect a similar action with all the other known members of the vitamin B complex, which have been shown to act as co-enzymes in bodily metabolic processes Spies and his associates<sup>21-23</sup> have shown, in a small series of cases, that 5-methyl uracil in large amounts can be substituted for pteroylglutamic acid in the treatment of macrocytic anemias Petering and Delor<sup>24</sup> have demonstrated that 5-methyl uracil will not restore growth or correct the hematologic disturbances in rats deficient in pteroylglutamic acid The explanation may be that a large number of natural and synthetic hematopoietically active substances exist Such substances may be related chemically, and their mode of action may be similar<sup>8</sup> On the other hand, it has been suggested that pteroylglutamic acid plays a role in nitrogen metabolism, for in rats casein affects a partial protective action against the production, by various sulfonamides, of signs of nutritional deficiency<sup>5, 15</sup>

These hypotheses leave much room for fundamental research, but there is more knowledge regarding the action of these hematopoietic substances in Addisonian pernicious anemia In studying this disease investigators have employed two methods of assessing the activity of pteroylglutamic acid and its related substances the hematologic response, including cytologic changes in the bone marrow, and the urinary excretion of pteroylglu-

tamic acid following oral or parenteral administration of this substance or its relatives

In patients with pernicious anemia in relapse a satisfactory remission can usually be produced with pteroylglutamic acid The hematopoietic response to the heptapeptide, pteroylheptaglutamic acid, depends on the amount of conjugase inhibitor in the preparation If the inhibitor content is high, there will be no change in the blood picture If, on the other hand, the inhibitor content is low, there may be a hematologic remission<sup>25</sup> These data suggest that the patient with pernicious anemia cannot utilize the heptapeptide owing to an inability to neutralize the activity of conjugase inhibitor In cases undergoing remission, there is a reticulocytosis followed by a gradual increase in the red-cell count and hemoglobin, together with a conversion of the characteristic maturation arrest of bone marrow into a normal cytologic picture<sup>2, 3, 11, 12, 25-31</sup>

What changes occur in urinary excretion of pteroylglutamic acid? Studies of this problem by Bethell and his associates<sup>25, 32</sup> are the most complete to date The investigators divided the subjects into three groups normal subjects, patients with pernicious anemia in relapse and patients with pernicious anemia in remission on liver Each of these groups was studied while the subjects were on a standard low-protein, meat-free diet of adequate caloric value, while the standard diet was supplemented with pteroylglutamic acid and while the standard diet was supplemented with yeast containing an equivalent amount of pteroylheptaglutamic acid In the last, a variety of preparations containing different amounts of conjugase inhibitor were tested In no case was any heptapeptide found in the urine Three significant observations were made In the first place the normal person excretes equal amounts of pteroylglutamic acid whether the diet is supplemented with pteroylglutamic acid or purified heptapeptide When, however, a preparation of heptapeptide containing a large amount of inhibitor is used as the supplement, the excretion of pteroylglutamic acid is reduced Secondly, the patient with pernicious anemia in relapse excretes much less pteroylglutamic acid than the normal subject when the diet is supplemented with either pteroylglutamic acid or purified heptapeptide If such a patient is given a heptapeptide preparation that is rich in inhibitor, there is practically no increase in the urinary excretion of pteroylglutamic acid over that occurring while he is on the standard diet When given liver extract along with heptapeptide high in conjugase inhibitor, the patient with pernicious anemia in relapse will show no increase in urinary excretion of pteroylglutamic acid Finally, the patient with pernicious anemia in remission on liver excretes about the same amount of pteroylglutamic acid while receiving this supplement as the normal subject does When given the heptapeptide in addition to conjugase inhibitor, he is able

to excrete much more pteroylglutamic acid than the patient in relapse.

Thus, the combination of liver extract and heptapeptide given to the patient with pernicious anemia in relapse does not cause an increased urinary excretion of pteroylglutamic acid. In a few patients with pernicious anemia in relapse receiving no supplement of heptapeptide, parenteral liver extract alone seems to cause a small but definite increase in the urinary excretion of pteroylglutamic acid.<sup>12</sup> This report has not yet been confirmed.

How are these preliminary metabolic studies to be interpreted? It appears that patients with pernicious anemia in relapse are unable to utilize pteroylglutamic acid because they are unable to neutralize the inhibitor. In contrast, patients in remission show marked improvement in their handling of heptapeptide. These observations are of interest, for studies *in vitro* have shown that the conjugase activity in tissues from patients with pernicious anemia is not significantly different from that of normal subjects.<sup>11, 12</sup> On the basis of the evidence so far available two interpretations have been offered. It has been suggested, on the one hand, that purified liver extracts contain substances that correct some abnormality in the conjugase enzyme system in patients with macrocytic anemias. The mechanism may be the removal of an inhibitor substance of conjugase or the providing of substances necessary for proper functioning of this enzyme system. Secondly, the metabolic derangement may be more deeply seated than mere inability to utilize the heptapeptide of pteroylglutamic acid.<sup>11</sup> Of great interest in connection with the interrelations between pteroylglutamic acid and liver extract is the recent experiment of Elvehjem and his co-workers,<sup>13</sup> who found that niacin-deficient dogs developed an anemia that ultimately failed to respond to niacin. No response to folic acid was noted, and refined liver extracts were effective only when the diets were high in casein or when supplements of pteroylglutamic acid were given. This point is more fully explained below.

#### PHARMACOLOGY AND TOXICOLOGY

Both in animals and in man pteroylglutamic acid and its relatives are nontoxic.<sup>14</sup> In animals these substances are not irritating when injected subcutaneously. They do not affect the blood sugar, and there is only a weak action on the isolated intestine. Respiration is not influenced, and the effects on the blood pressure are minor. In long-term experiments, the daily intraperitoneal administration of 5 mg per kilogram of body weight for two months produced no unfavorable reactions in rabbits and rats. In a similar period, daily peritoneal injections of 50 mg per kilogram of body weight to rabbits and 75 mg per kilogram of body weight to rats caused minor changes in the kidney tubules but no deaths. The acute toxicity for ex-

perimental animals is low. The LD<sub>50</sub>\* for mice is 600, for rats, 500, for rabbits, 410 and for guinea pigs, 120 mg per kilogram of body weight.

In human subjects oral or intramuscular administration is essentially without toxic effects. Up to 150 mg has been given intramuscularly, and 500 mg orally in a single dose. Intravenous medication, on the other hand, is not recommended, for in a few cases rapid intravenous administration of 150 mg of pteroylglutamic acid has resulted in a shock-like reaction. The pulse has disappeared, the blood pressure has fallen, and unconsciousness has ensued. Fortunately, recovery has always followed within several minutes, although headache and nausea have persisted for as long as twenty-four hours. This shock-like reaction may, however, be due to impurities in the synthetic preparations.<sup>11</sup>

The therapeutic dosage currently recommended by most authors is 10 mg daily by mouth.<sup>27, 27, 28</sup> For maintenance, 5 to 10 mg usually suffices. In any case these doses may be varied depending on the individual case. Davidson and Girdwood<sup>27</sup> suggest that if clinical and hematologic responses do not occur within two weeks, it can be assumed that the disease being treated is not due to a deficiency of pteroylglutamic acid and that continued administration of the vitamin is contraindicated.

\*LD<sub>50</sub> represents the amount of pteroylglutamic acid (mg. per kilogram of body weight) that will kill 50 per cent of the animals within the test period.

#### (To be concluded)

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*BENJAMIN CASTLEMAN, M.D., *Associate Editor*EDITH E. PARRIS, *Assistant Editor*

### CASE 33441

#### PRESENTATION OF CASE

*First admission* A fifty-nine-year-old married Italian laborer was admitted to the hospital because of back pain.

Five months before admission the patient was first seen in the Out Patient Department because of pain in the left sacroiliac region, which had begun two and a half months previously while he was shoveling in a gravel pit. He admitted that similar brief attacks had occurred for about six months, but these had always cleared spontaneously. For the past two and a half months, however, the pain persisted despite strapping, heat, massage and rest. He also complained at bedtime of intermittent attacks of numbness over the outer aspect of the left thigh and an occasional sharp shooting pain from the left sacroiliac joint to the knee over the outer aspect of the thigh. He walked with a lump, used a cane and could produce only slight movement of the lumbar spine. An x-ray film at that time revealed moderate degenerative hypertrophic changes. There was no destructive or developmental abnormality. Conservative therapy was of no avail. The spinal fluid and a myelogram one month before entry failed to show any abnormalities. The patient continued to complain of the same difficulties and had lost 30 pounds of weight. During the week before entry a small nodule, 1.5 by 2.5 cm., appeared in the region of the upper third of the left sacroiliac joint and was firm and tender and caused reproduction of the referred pain and numbness along the anterolateral aspect of the left thigh.

Physical examination revealed that bending in any direction caused pain. Straight-leg raising was possible from 38 to 50° with tight hamstrings. Coughing and sneezing caused no pain. The reflexes were equal and hypoactive bilaterally in the legs. There was local tenderness over the lumbar and left sacroiliac regions. Recent weight loss was evident. The scleras were slightly icteric. There was deep tenderness in the right upper quadrant, with a palpable liver edge 2 cm. below the costal margin on deep inspiration and the upper edge

percussed at the top of the sixth rib. A questionable, deep, irregular, poorly defined mass was noted in the right upper quadrant and right paraumbilical region. The spleen was questionably palpable.

The blood pressure was 160 systolic, 95 diastolic. Examination of the blood showed a red-cell count of 4,870,000, with 85 per cent hemoglobin, and a white-cell count of 8400, with 62 per cent neutrophils. The urine was normal.

Liver-function tests were negative except for a ++++ cephalin-flocculation test in twenty-four and forty-eight hours and a van den Bergh reaction of 1.2 mg. per 100 cc. direct and 2.3 mg. indirect. A plain film of the abdomen revealed a liver somewhat smaller than that usually expected and a spleen within normal limits. A gastrointestinal series was normal. Barium enemas were not totally satisfactory because of pectenosis, but no definite abnormality was seen. Three weeks after admission the van den Bergh reaction fell to 0.5 mg. per 100 cc. direct and 0.9 mg. indirect. A cephalin-flocculation test was ++ in twenty-four hours and +++ in forty-eight hours. An intravenous pyelogram revealed normal kidneys, but the third lumbar vertebra at its left lateral aspect showed a loss of normal outline, with an irregular, moth-eaten appearance at this portion of the body, and the left transverse process suggested destruction. Also, there was loss of the articular facet on the left. The left psoas shadow appeared to bulge slightly opposite the lesion. No other destructive areas were seen. Alkaline and acid phosphatase levels were normal. An aspiration biopsy of the lumbar vertebra revealed a malignant tumor, unclassified, with a question of liposarcoma. X-ray therapy was instituted for relief of the pain with good success and some sclerosis of the lumbar vertebra. The patient was discharged two months after admission.

*Final admission* (two years later) He was seen in the Out Patient Department ten months after discharge, when there appeared to be no progression of the destruction of the left third lumbar vertebra but rather some evidence of further recalcification. A month later, however, the jaundice, which had disappeared for a while, recurred and began to increase. The patient developed lower abdominal pain, and his appetite became poor.

It was discovered on this admission that in his early youth he had been a heavy drinker, averaging 12 to 18 bottles of beer daily, with occasional wine or whisky for many years and irregular eating habits at that time. About thirty years previously he had had an attack of fairly marked jaundice with itching, which had subsided completely on medical treatment. Since then he had had occasional bouts of dark urine, and he believed that his eyes may have been yellow from time to time.

Physical examination disclosed an intensely icteric man with a smooth fine skin, rather sparse hair and scattered spider telangiectases over the

chest and back. The liver edge was palpable 7 cm below the costal margin. There was no evidence of ascites. The liver was questionably slightly nodular. There was slight tenderness over the lumbosacral joint.

The blood pressure was 134 systolic, 78 diastolic.

Examination of the blood revealed a red-cell count of 4,830,000, with 10.5 gm of hemoglobin, and a white-cell count of 4600, with 86 per cent neutrophils. The urine gave a + test for albumin, and the sediment contained cellular casts. The alkaline phosphatase was 13.7 units per 100 cc. The bromsulfalein test disclosed 100 per cent retention of the dye. The total protein was 7.68 gm per 100 cc, with 3.88 gm of albumin and 3.80 gm of globulin, the nonprotein nitrogen was 28 mg, and the fasting blood sugar 158 mg per 100 cc. A cephalin-flocculation test was ++++ in both twenty-four and forty-eight hours. The prothrombin time was 42 seconds (control, 15 seconds). The acid phosphatase was 1.5 units per 100 cc.

An x-ray film of the chest revealed evidence of old pleurisy at the left costophrenic angle and an area of increased density, 3 mm in size, in the left third interspace that might have been a blood vessel but could have been a small metastatic nodule. Marked arthritic changes were noted in the dorsal spine, a defect in the body of the third lumbar segment remained unchanged, and a soft-tissue mass still distorted the left psoas muscle. There seemed to be a mass in the epigastrium, which might have been the liver. In the hospital the prothrombin time rose, the patient developed guaiac-positive stools, and the nose began oozing blood. He developed complete anorexia to the point of nausea and had severe lower abdominal pain. He became anuric, and on the fifth hospital day the prothrombin time was 84 seconds against a 15-second control. On the sixth hospital day he developed a strong cholemic odor, became totally unresponsive and died.

#### DIFFERENTIAL DIAGNOSIS

**DR WILLIAM CLARK** It is quite apparent that this patient had severe liver disease and that involvement of that organ had been present, at least in recurrent form, for a thirty-year span. The terminal illness was one of liver failure, with associated renal involvement. In addition there was an episode of back pain, which was explained by the finding of a neoplasm involving the lumbar spine, two years before the final admission.

May we see the x-ray films?

**DR MILFORD D SCHULZ** The only available films of the spine are those made after x-ray therapy, so that I cannot say how the bones looked before treatment. The sclerosis that can be seen is probably the result of treatment. I can only point out the area of destruction in the third lumbar segment involving the small parts of the vertebra as well as

its body. The soft tissue in the left psoas region bulges and displaces the ureter. I do not know whether the shadow described in the lung represents a metastatic nodule or not. The only other thing that might be mentioned is the fact that these films of the esophagus are not adequate to allow one to say that the patient did not have varices. Nor does there seem to be a mass extending through the diaphragm from the liver.

**DR CLARK** We do not have the necessary films to help us determine the size of the liver or whether the mass was part of the liver. I should like to ask about the tumor. It is too bad that we do not have the older films. Are you reasonably certain that the tumor arose in the lumbar vertebrae and extended into the psoas region, or is it possible that it invaded the vertebrae from without?

**DR SCHULZ** I think that the latter is a possibility, but something arising in the vertebral body seems likelier. The whole affair could be a metastatic tumor.

**DR CLARK** Do you think that it is unusual for metastatic tumors of the lumbar spine to break through and invade into the soft tissue?

**DR SCHULZ** It is rare, but not impossible.

**DR CLARK** Primary tumors of the lumbar spine are not common. Most of the tumors of this area are metastatic lesions. I think we can safely assume that the predominant symptomatology at the first admission can be explained by the neoplasm. The pathological report of the nature of the neoplasm is difficult to evaluate. The tumor could not be definitely classified, as the pathologist stated, and I assume that it had many of the characteristics of a liposarcoma — a diagnosis that in itself, as I understand it, is usually made with some hesitation. At least in a case reported here in 1942,\* Dr Mallory offered some apologies when he made the diagnosis of liposarcoma. Liposarcomas are reported to be radiosensitive, and I assume that there is good x-ray evidence that this tumor was radiosensitive. In addition, the symptoms improved. There is very little more that I can say about the diagnosis other than to accept it. The diagnosis is a reasonable explanation for the back pain. It is interesting that among the liposarcomas that are described, some start in a bone and invade the soft tissue and have been mistaken for soft-tissue tumors at operation. They are also said to be encapsulated. The problem is how to evaluate the tumor in relation to the liver disease.

The presence of both severe liver disease and a malignant tumor makes one want to conclude that this patient had a tumor in the liver, with metastases to the spine, or tumor of the spine metastasizing to or encroaching on the liver tissue and producing liver failure. I can find nothing in the protocol that will support either hypothesis, and I shall

\*Case records of the Massachusetts General Hospital (Case 10057). *New Eng J Med* 226:204, 1942.

consider two separate diseases. The patient had had liver disease at twenty-nine years of age. I prefer to postulate two separate entities rather than two different types of liver disease. I shall try to develop the hypothesis that he had cirrhosis, that will make it easy to assume that the tumor did not metastasize to the liver, because we know that such metastasis does not usually take place.

In looking back through the record we have to deal with seemingly repeated episodes of jaundice, although we have only one clear-cut story. The history is also complicated by the fact that the patient consumed a large amount of alcohol. We do not associate alcohol consumption with acute episodes of hepatitis accompanied by jaundice, but rather with insidious changes characterized by fat being deposited in the liver that in some manner is related to nutrition. The best conclusion that we can draw regarding the episode of jaundice at the age of twenty-nine is that he had hepatitis of a cholangitic type as evidenced by the itching. Then we are told that following this he had episodes in which the urine was dark and that he probably had jaundice. I assume that these episodes were recurrences of the phenomenon that appeared at the age of twenty-nine.

He had jaundice at the time of the first admission to the hospital and at that time the liver was palpable but was not considered to be enlarged by the radiologist. Although one can conclude that he had some form of active liver disease, the tests performed at that time and the physical findings do not lead one to make a diagnosis of cirrhosis. After a remission of symptoms and physical signs he again exhibited signs of severe liver damage at the time of the final admission, and telangiectases or spider nevi were also found. The liver was described as enlarged and somewhat nodular, and I shall conclude that if nodules could be felt the liver was likewise firm. Even on the last admission, careful analysis revealed very little with which to make a diagnosis of cirrhosis of the liver. Perhaps the physical findings were the only things that definitely lead in that direction. The liver tests showed severe liver damage, but I do not believe that the tests in themselves imply cirrhosis. The repeated episodes of hepatitis with jaundice, which I believe to have been associated with cholangiolitis and eventual liver failure, make me want to explain the whole picture by a type of cirrhosis that developed in the course of recurrent cholangiolitic hepatitis. The concept of the recurrent type of cholangiolitic hepatitis and cirrhosis may not be generally acceptable but offers a good explanation of the sequence of events in this patient. I do not want to make a diagnosis of alcoholic cirrhosis, but we must admit that alcohol in some way influenced the liver damage. In other words, I do not believe that this picture will be that of alcoholic cirrhosis from the standpoint of the pathologist or a fatty

type of liver. The liver tests indicated terminal liver damage. The severe jaundice and the elevation of prothrombin time associated with the hemorrhage, the positive cephalin-flocculation test and so forth enable one to say that the patient died in liver failure. He developed terminal uremia, and nothing more about that can be said other than that he probably developed bile nephrosis.

I should like to conclude that he had cirrhosis associated terminally with an acute hepatitis, cholangiolitic in type, bile nephrosis and liposarcoma of the spine and the psoas region. I cannot say whether or not this tumor invaded the region of the liver because I do not have the evidence to make such a statement.

#### CLINICAL DIAGNOSES

Cancer of liver  
Obstructive jaundice

#### DR. CLARK'S DIAGNOSES

Cirrhosis of liver  
Bile nephrosis  
Liposarcoma of spine

#### ANATOMICAL DIAGNOSES

*Hepatoma, with invasion of cystic duct and metastasis to third lumbar vertebra*  
Cirrhosis of liver  
Bile nephrosis  
Arteriosclerosis, generalized, moderate

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY. The slide of the biopsy in this patient was shown to a number of pathologists, and there was no general agreement concerning diagnosis. The outstanding feature of the histologic picture was a marked fatty vacuolization of the tumor cells, but on the other hand fat can be present in tumors for a number of reasons. The presence of fat does not prove that one is dealing with a liposarcoma. I did not see the slide until relatively recently and made a rather lucky guess on looking at it. I suggested that it might be a hepatoma. I know of a case in which the diagnosis of hepatoma was made from bone metastasis four years before the patient died and subsequently confirmed. In this case the interval was shorter but still significant—about two years.

Autopsy showed cirrhosis of the liver, which was rather finely granular in type, with a few large nodules and obvious invasion of the portal and hepatic veins with tumor thrombi—a characteristic behavior pattern of the primary liver-cell tumor. There was also involvement of the lymph nodes in the porta hepatis, from which the tumor had extended into the wall of the cystic duct and ulcerated so that fresh hemorrhage filled the biliary tract. The only other nodule of tumor found was in the lumbar vertebra, where it was originally seen by



x-ray study It was by that time a rather large tumor mass, which had destroyed a large part of the vertebra and had extensively invaded the psoas muscle on one side Microscopically, the tumor cells showed the usual arrangement seen in hepatomas, with numerous, huge tumor giant cells, which often contained 50 or 60 nuclei, a characteristic feature of primary tumor of the liver

DR CLARK Metastatic hepatoma of the spine must be unusual Would you say that that is true, Dr Mallory?

DR MALLORY The major metastases of hepatoma are by way of the blood stream rather than the lymphatic vessels, although local lymph-node involvement may occur The most frequent focus for metastasis under these conditions is naturally in the lungs In this case the tumor seems to have passed through the lung without causing a gross lesion Occasionally, as in hypernephroma, another blood-borne tumor, one sees similar bone metastases without demonstrable pulmonary lesions

A PHYSICIAN How often is this type of tumor found?

DR MALLORY: We used to consider it very rare Today it is not uncommon There are parts of the world where it is one of the most frequent tumors, especially South Africa and Java It is still relatively uncommon here One almost never sees it except subsequent to a long-standing cirrhosis. I think that as our treatment of cirrhosis improves and we keep patients alive longer and longer, we shall see this tumor with progressive frequency

DR M M SUZMAN In South Africa we have always found it associated with cirrhosis

DR MALLORY The only other notable relation is with fluke infestation

DR WILLIAM McK JEFFRIES Is hepatoma as radiosensitive as the tumor in this case?

DR MALLORY I cannot answer that I do not believe that we have treated many hepatomas except in such terminal stages that there was no possibility of determining whether they were radiosensitive or not. Usually, by the time the diagnosis is made, the patient is almost moribund. Do you agree to that, Dr Schulz?

DR SCHULZ I think that we treat them only by accident.

A PHYSICIAN What is the explanation of the terminal uremia?

DR MALLORY That was a severe grade of bile nephrosis

## CASE 33442

### PRESENTATION OF CASE

A forty-eight-year-old housewife was admitted to the hospital because of pain in the back and weakness of both legs

The patient stated that as a young woman she had had pains in the lower back that sometimes

limited activity The pain was again pronounced when she was pregnant seventeen years previously Beginning six and a half years before entry there was almost constant pain on the left side in the lower back, hip, anterior aspect of the thigh and leg, heel, sole of the foot and in all five toes An operation for an intervertebral disk at the fourth and fifth lumbar region was performed five years before entry. The patient was free from pain until she started working again as a pianist, four months after the operation, when the same pain returned, steadily increasing in severity, and was shortly accompanied by some dragging of the left leg One month before admission the right leg became weak The weakness of both legs increased, and on admission the patient was able to walk only by using a cane and with the help of another person Slight difficulty in voiding had been present for several days

Physical examination revealed a well nourished woman in no obvious discomfort The heart and lungs were normal There was a low lumbar midline scar Both legs were weak and spastic, the right more so than the left The feet could be dorsiflexed just short of right angles The knee jerk was absent on the left and present on the right There was bilateral ankle clonus Abdominal reflexes were absent, and ankle jerks were brisk, the plantar reflexes were extensor Pain, touch and temperature sensation were impaired on the legs, posterior portions of the thighs and saddle area, but no sharply defined sensory level was demonstrated There was diffuse tenderness over the lumbar spine and sacrum

The urine had a specific gravity of 1.002, and the sediment contained occasional pus and epithelial cells Examination of the blood disclosed 13.8 gm of hemoglobin and a white-cell count of 8300

A spinal puncture was performed in the third lumbar interspinous space On jugular compression the pressure rose slowly from 150 to 350 mm of water and fell very slowly to 250 mm when compression was released The protein was 204 mg per 100 cc X-ray examination showed an operative defect in the upper margin of the left lamina of the fifth lumbar vertebra, and degenerative changes about the smaller articulations between the fourth and fifth lumbar vertebrae

A myelogram was done on the second hospital day The oil passed up to the body of the twelfth thoracic vertebra, where it was completely arrested, ascending slightly higher on the right and forming a fairly good "cap" (Fig 1) On the fourth hospital day an operation was performed

### DIFFERENTIAL DIAGNOSIS

DR ARTHUR L WATKINS May we see the x-ray films?

DR TOUFIC KALIL There is no mention in the abstract of the fracture of the seventh thoracic

vertebra, and the myelogram shows this round irregular defect with complete blockage at the level of the twelfth dorsal vertebra. Reference to the other end of the Pantopaque column is seen here, with the block at the lower end, occurring at the fifth lumbar interspace, and with some irregularity of the lamina on the left, probably from the old operation.

Dr WATKINS Do you see any evidence of destruction of the vertebra at the twelfth dorsal vertebra?

Dr KALIL No.

Dr WATKINS We have a history of intermittent complaints relative to the back, extending over a long period, with an increase in symptoms during pregnancy. The character of the pain became persistent about six and a half years before the final episode. At the time of the first operation there were sensory symptoms referable to the lower lumbar and first sacral segments, and presumably on this basis the operation was done for a protruding intervertebral disk. We do not have any further information about what was found, but we do know that as soon as activity was started again the pain returned, and for the first time we find evidence of definite involvement of the motor system, manifested by a dragging of the left leg. We should like to know what was the type of weakness — whether it was on the basis of anterior-root involvement, that is, the lower motor neuron type of weakness, or due to disease in the spinal cord, with some spasticity present, again, we can only guess about that. What finally brought the patient to the hospital was increase in pain and involvement of the opposite extremity.

Physical examination made it perfectly evident that we must go higher than the site of the previous operation to explain the physical signs: the spastic type of weakness, with Babinski response, ankle clonus and absent abdominal reflexes. A spinal puncture was done above the level of the previous operation, and there was block higher up as judged from the dynamics and also increased protein, so that we now look for a lesion in the lower part of the spinal cord. Although the sensory level was not very accurate, we suspect clinically from the physical findings involvement presumably of the first sacral segments, and we localize a lesion right at the end of the spinal cord to explain the present complaints.

Regarding the etiology of such a lesion, first of all we might consider the long history of back pain. This may simply have been a poor back mechanically. It is difficult to interpret from the x-ray film after the operations what sort of fault was present in the lumbosacral region. Frequently in pregnancy a patient with rheumatoid arthritis gets increase in back pain, but the sacroiliac films do not show any evidence of it, and we would expect after all these years to have definite x-ray evidence

if it had been due to rheumatoid arthritis. This patient may have had pain for mechanical reasons and a ruptured disk to explain some of the symptoms, but the picture of a slowly increasing involvement of the spinal cord cannot be reasonably explained by a ruptured disk. I do not know how to link up what appears to be an old compression fracture in the dorsal area. We have no history of trauma above the level of the lesion that seemed to



FIGURE 1

be producing the symptoms, so that I am inclined to overlook that because there is no x-ray evidence of neoplasm.

Considering infection as a possible cause, we have nothing to suggest syphilis. Tuberculosis can of course cause spinal-cord compression, but if it were of such long standing we would expect a soft-tissue mass and some bony changes, which were absent, and I therefore think that we can rule out tuberculosis. Another possibility is arachnoiditis, which is sometimes given credit for intermittent and prolonged symptoms in numerous areas, but I would not expect it to cause an x-ray picture such as this, with so definite a block at one level. Again, arachnoiditis is not too satisfactory a pathological

diagnosis, and I do not believe that that is the answer in this case

That leaves us with tumor of some sort as the most probable diagnosis. This was a slowly growing tumor with a history of at least six years' duration. If we localize it at the end of the spinal cord we can only guess what type of tumor it might have been. There is no evidence of metastatic disease or primary bone tumor, so far as I can see. I shall choose as my first guess an ependymoma of the conus or filum, which is slowly growing, or possibly a meningioma.

DR AUGUSTUS ROSE: Do you think that she had a ruptured intervertebral disk?

DR WATKINS: Yes, she may have had a ruptured disk, but I doubt whether it was responsible for the complaints, particularly if the weakness was spastic and developed immediately after operation.

DR ROSE: Was a myelogram done before the operation for ruptured disk?

DR CHARLES S. KUBIK: No, it was not.

Dr Ballantine, will you describe the operative findings?

DR H. THOMAS BALLANTINE, JR.: This patient was operated on under nitrous oxide, oxygen and ether anesthesia, and a laminectomy was done including the tenth, eleventh and twelfth dorsal vertebrae just above the conus of the cord. The cord was found to be considerably widened, owing to diffuse swelling, more on the left than on the right, bearing out the x-ray findings that the block started slightly lower on the left side than on the right. I shall quote part of the operative note because it is interesting: "On opening of the dura the tumor could be seen bulging from the left posterior surface of the cord as a rounded purple-pink mass. There was considerable fusiform swelling of the cord above and below the tumor." The tumor seemed to start in the substance of the cord and seemed at first to be an intramedullary glioma, although against that was the fact that there was a discrete mass, which was removed almost as a dumbbell-shaped tumor. We got part of it out — a piece measuring about 1.5 cm in diameter — and thought that that was all until further dissection showed below this layer another mass 2 cm in diameter. At the time of operation there was no clue regarding the point of origin of this new tumor mass.

DR KUBIK: What is the present condition of the patient?

DR BALLANTINE: Postoperatively she had difficulty in voiding and marked increase in weakness in the legs. A week after operation these symptoms began to clear, and she developed fairly good tone in the right leg beginning at the ankle and the toes and some extension and dorsiflexion. The left leg was much slower in returning to normal. On intensive physiotherapy she reached the point where at discharge from the hospital, approximately a month later, she was able to bear weight on the left leg and quadriceps function was returning. I think that she will walk. The plantar signs cleared, and she had only occasional incontinence at night and was never incontinent during the day.

#### CLINICAL DIAGNOSIS

Tumor of spinal cord, eleventh dorsal region

#### DR WATKINS'S DIAGNOSIS

Ependymoma of conus?

Meningioma?

#### ANATOMICAL DIAGNOSIS

*Meningioma of spinal cord*

#### PATHOLOGICAL DISCUSSION

DR KUBIK: I suppose that it would be difficult to say whether or not this patient had a ruptured disk at the time of the original operation. The pain was the type caused by ruptured disk, and I should say less commonly observed with lesions as high as this. It seems likely that in this case the symptoms were caused by the tumor. The case illustrates the importance of careful clinical investigation.

DR BALLANTINE: There is some evidence that this tumor was responsible for all the symptoms in that the back pain, of which the patient had complained for six and a half years, was relieved soon after the operation.

DR KUBIK: The tumor was a meningioma. At operation it was thought that ependymoma was the more probable diagnosis. This is a common site for ependymomas, arising in the lower part of the cord or conus. Dr W. Jason Mixter, as I understand it, did not find any attachment to the dura.

DR BALLANTINE: No attachment was found.

DR KUBIK: Histologically, the tumor was a typical meningioma.

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## APPOINTMENT OF NEW EDITOR

The Committee on Publications of the Massachusetts Medical Society takes pleasure in announcing the appointment of Dr. Joseph Garland as Editor of the *New England Journal of Medicine*.

RICHARD M. SMITH, *Chairman*

## CHILD HEALTH SERVICE FOR STUDENT VETERANS

PLANS for the care of approximately 1500 children of student veterans at Harvard have finally matured and were put into operation in mid-September. The project, which has been under consideration for a year or more, is based primarily on an urgent pediatric need. There have been at Harvard for the past two years, living in student housing facilities in Cambridge and at Harvard Village in

Ayer, some 3000 GI families from all parts of the country, subsisting mainly on government allotments insufficient to provide adequate medical care for their children. This unusual concentration of infants and children, moreover, was beginning to overtax the medical facilities of the community and contained the possibility of serious difficulties in case disease should appear in epidemic proportions.

The need and the danger have been apparent to Dr. Arlie V. Bock, professor of hygiene at Harvard University, who enlisted the aid of Dr. Allan M. Butler, chief of the Children's Medical Service at the Massachusetts General Hospital and professor of pediatrics at Harvard Medical School. The plan that has gone into operation resulted.

Two health centers for the children involved have been opened, one in Cambridge and one in the Lovell General Hospital at Fort Devens. At these centers, under the direction of Dr. Francis C. McDonald, medical service, comprising physical examinations, immunizations, diagnosis and treatment, is being provided at federal expense. Home service is provided as needed, including consultation visits by pediatricians who are licentiates of the American Board of Pediatrics.

Harvard University provides clinic and office space, the Massachusetts General Hospital furnishes administrative services and clinical facilities and personnel, and the Massachusetts Department of Public Health aids in the administrative program, supervises the public-health nursing and provides consultative service on nutrition and medical social problems.

Last but not least, funds, based on a cost of \$35 per patient per year are being provided by the Children's Bureau of the United States Federal Security Administration, via the Massachusetts Department of Public Health. These funds are available on the stipulation that they shall be used for a study as well as for a service project.

The service project has been outlined above. The study will consist largely in the collection and compilation of "statistics on the cost of providing complete health and medical care for infants and children as well as on the incidence of various illnesses and the kinds of service required." As such it should prove to be a valuable complement

to the survey of pediatric facilities of the country that has been undertaken by the American Academy of Pediatrics and is now drawing to its close

There appears to have been launched, under excellent auspices, a particularly worthy government-financed project. Only one similar program has been conducted, that which was under way last year at the University of Washington, in Seattle. The medical profession at large should heartily approve of such a public-health and fact-finding undertaking.

### STREPTOMYCIN IN BACTERIAL ENDOCARDITIS

CASES of bacterial endocarditis, irrespective of their etiology, were almost universally fatal prior to the introduction of the newer chemotherapeutic and antibiotic agents. The use of sulfonamides has resulted in cures only in rare cases. On the other hand, there is now a considerable body of evidence to show that penicillin is highly effective in the treatment of most cases of subacute bacterial endocarditis and has also produced cures in an appreciable proportion of cases of acute bacterial endocarditis due to penicillin-susceptible organisms.

There remains, however, a group of cases of acute and subacute bacterial endocarditis due either to streptococci that are relatively insensitive to penicillin or to gram-negative bacilli, which are quite resistant to the action of that antibiotic. Most of the latter organisms and some of the former are susceptible, at least in vitro, to streptomycin. It therefore seems reasonable to attempt prolonged and intensive streptomycin therapy in such cases.

The ease with which resistant variants appear in patients with various infections during the course of treatment with streptomycin, thus nullifying the effects of that antibiotic, and the nature of the lesion in cases of bacterial endocarditis may give rise to reasonable doubts concerning the effectiveness of prolonged and intensive treatment with streptomycin, particularly since irreversible deafness and vestibular damage occur in most cases. Such therapy can be justified, even in such a fatal disease, only if there is a reasonable expectation of cure of the underlying infection in a significant proportion of cases.

It is therefore gratifying to have a report summarizing the results of the use of streptomycin in the treatment of bacterial endocarditis. Hunter<sup>1</sup> reviewed the cases that have been treated at the Presbyterian Hospital, together with those collected by Dr. Chester S. Keefer and the Committee on Chemotherapeutic and Other Agents of the National Research Council. Of a total of 18 patients with bacterial endocarditis treated with streptomycin, 8 appeared to be cured. The cures included 4 of 8 cases in which a gram-negative bacillus was involved, 1 of 5 cases due to enterococci, 2 of 4 cases in which *Streptococcus viridans* was the organism and 1 case due to *Staphylococcus aureus*. Penicillin was also used, apparently without success, in the cases in which the gram-positive organisms were involved, and sulfonamides were used in some of the cases. One additional case of bacterial endocarditis due to a parainfluenza bacillus and apparently cured by streptomycin has recently been reported from the Massachusetts General Hospital.<sup>2</sup>

In some of the cases included in Hunter's report, failures were probably the result of treatment that was inadequate or was begun late in the course of the disease. The fact that an appreciable percentage of cases resulted in cures, however, indicates that streptomycin therapy is warranted in all cases of bacterial endocarditis due to gram-negative bacilli and in those due to other organisms that are sensitive to streptomycin in which the patient fails to respond to penicillin. The results in these cases also emphasize the importance of careful bacteriologic control in the management of such cases.

#### REFERENCES

1. Hunter, T. H. Use of streptomycin in treatment of bacterial endocarditis. *Am. J. Med.* 2:436-442, 1947.
2. Cases from the Medical Grand Rounds, Massachusetts General Hospital. *Am. Practitioner* 1:498-504, 1947.

### MASSACHUSETTS MEDICAL SOCIETY DEATHS

**NELSON** — Christian A. Nelson, M.D., of Cambridge, died on September 21. He was in his seventy-fourth year. Dr. Nelson received his degree from Harvard Medical School in 1911. He was a former member of the Massachusetts Medical Society. His widow survives.

**UNDERHILL** — Elizabeth C. Underhill, M.D., of Poughkeepsie, New York, died on September 20. She was in her seventy-seventh year. Dr. Underhill received her degree from Cornell University Medical College in 1900. She was resident physician at Mt. Holyoke College for thirty-seven years.

## ELLIOTT CARR CUTLER (1888-1947)

Elliott Carr Cutler was born in Bangor, Maine, on July 30, 1888, the son of George Chalmers Cutler and Mary Wilson Cutler. After his graduation *cum laude* from Harvard Medical School in 1913 he spent some months in Dr. Frank B. Mallory's laboratory, and then studied at the University of Heidelberg. He was surgical house officer at the Peter Bent Brigham Hospital from 1913 to 1915, and then resident surgeon at the Massachusetts General Hospital.

Dr. Cutler served in France in 1915, with the Harvard Unit, before the United States entered the war, his second tour of duty began in May, 1917, when he again went to France with Base Hospital No. 5. He was promoted to the rank of major in November, 1918, and received the Distinguished Service Medal.

On his return to the United States Dr. Cutler was resident surgeon at the Peter Bent Brigham Hospital from August, 1919, to September, 1921, associate in surgery at the hospital and chairman of the Department of Surgery, Harvard Medical School. In 1924 he was called to the professorship of surgery at Western Reserve University School of Medicine, Cleveland, where, in addition, he was director of the Surgical Service of the Lakeside Hospital. In 1932 he was chosen to succeed Dr. Harvey Cushing as Moseley Professor of Surgery at the Harvard Medical School and surgeon-in-chief of the Peter Bent Brigham Hospital.

Before the United States entered World War II, Dr. Cutler reorganized General Hospital No. 5, with which he had served in 1918. He was chief surgical consultant of the European Theater of Operations from August, 1942, to February, 1945, when he became Chief of the Professional Services Division in that Theater. He was promoted to a brigadier-generalship in June, 1945, and received an Oak Leaf Cluster to the Distinguished Service Medal already awarded. He was made honorary officer of the Most Excellent Order of the British Empire and received the *Croix de Guerre* with palm from the French Government and the Haakon VII Liberation Cross from the King of Norway.

At the time of his death he was president of the American Surgical Association — perhaps the highest honor that can be granted to any American surgeon. In 1947 he received the Bigelow Medal from the Boston Surgical Society. He was a member of the Society of Clinical Surgery, the New England Surgical Society, the American Association for Thoracic Surgery, the American Committee for the Protection of Medical Research,



the Society for Experimental Biology and Medicine and the American Society for Clinical Investigation and honorary member of surgical societies of France, Italy and Belgium and was given honorary fellowships in the Royal College of Surgeons of England, the Royal College of Surgeons of Edinburgh and the Royal Society of Medicine of England. He had received honorary degrees from the University of Strasbourg, the University of Vermont and the University of Rochester.

He was on the editorial boards of the *Journal of Clinical Investigation*, the *American Journal*

of Surgery, the *American Heart Journal* and the *British Journal of Surgery*.

The obituary notice of the *British Medical Journal* (August 23, 1947) contained the following note, written by his friend and associate, Sir Gordon Gordon-Taylor: "Elliott had always driven the chariot of his busy, feverish life with rein unchecked, not one moment of the day wasted, no evenings 'steeped in homed indolence'. Even when the truth of his mortal illness came 'naked and sabre-like' against his great heart the pace of life never slackened. There was no neglect of the surgical direction of his hospital, he travelled all over the wide areas of the United States of America in his supreme desire that the surgical arrangements and the surgery for the veterans of the recent war should be the very best. The term 'deputy' found no place in his vocabulary. No complaint of the unkind blow of Fate ever passed his lips, the courage of the man evoked admiration on every hand."

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	November 3	Paul W. Hugenberger
Haverhill	November 5	William T. Green
Lowell	November 7	Albert H. Brewster
Brockton	November 13	George W. Van Gorder
Gardner (Worcester Subclinic)	November 18	John W. O'Meara
Springfield	November 18	Garry deN. Hough, Jr.
Pittsfield	November 19	Frank A. Slowick
Hyannis	November 20	Paul L. Norton
Worcester	November 21	John W. O'Meara
Fall River	November 24	David S. Grice

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments

## CORRESPONDENCE

### CONTRACEPTIVE CARE TO MARRIED WOMEN

*To the Editor* An initiative petition seeking adoption of "An Act to Allow Physicians to Provide Medical Contraceptive Care to Married Women for the Protection of Life or Health" was filed the end of July, 1947, by the following petitioners: Karl T. Compton, president of Massachusetts Institute of Technology, Dr. Nathaniel W. Faxon, medical director, Massachusetts General Hospital, Dr. Robert H. Goodwin, obstetrician-in-chief, St. Luke's Hospital, New Bedford, Dr. Frederick C. Irving, professor emeritus of obstetrics, Harvard Medical School, Henry P. Kendall, of Sharon, president of Kendall Company, Dr. Samuel A. Levine, assistant professor of medicine, Harvard Medical School, Mrs. Arthur Devens Potter, of Greenfield, past president, Massachusetts State Federation of Women's Clubs, Dr. John C. Rock, clinical professor of gynecology, Harvard Medical School, Mrs. Arthur G. Rotch, former president of Massachusetts League of Women Voters, and Dr. George M. Shipton, chief of Obstetrical Department, House of Mercy Hospital, Pittsfield.

In submitting the petition, President Compton made the following statement:

I believe that the public interest can best be served by placing in medical hands the control of medical matters. The giving of contraceptive care is a generally accepted medical technique which should not be denied by law to anyone whose medical need is great. Those needing and desiring contraceptive help should not be either left in complete ignorance or left at the mercy of irresponsible sources of information. Naturally, such information and help should not be forced upon anyone whose religious beliefs are opposed to those measures, but by the same token the religious beliefs of some should not be forced upon all. This is an elementary matter of civil liberties in a democracy.

With this statement I am in entire accord.

The petition has been approved by the Attorney General as to form and substance, and a minimum of 20,000 certified signatures of registered voters must be obtained this fall. The measure then goes to the Legislature, which must act by roll-call vote before June, 1948. If not enacted into law by the Legislature, the measure goes on the 1948 ballot as a referendum after the collection of a minimum of 5000 additional signatures.

A similar measure was rejected by a small margin of voters in 1942 after a vigorous campaign that aroused widespread interest and resulted in a larger number of votes being cast than on any previous referendum. At that time, the Massachusetts Supreme Judicial Court, in an advisory opinion, stated that such a measure was "purely permissive (and) will not interfere with the freedom of any person within its scope to act in strict accordance with his religious views."

Only Connecticut and Massachusetts now prohibit doctors from prescribing contraception for their sick patients, al-

though the American Medical Association and other medical groups have recognized the procedure as an integral part of preventive medicine.

I urge all physicians to support this measure and to help in obtaining the necessary number of signatures.

ROBERT L. DENORMANDIE, M.D.

Lincoln

## NOTICES

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 6

FRIDAY, NOVEMBER 7	
*10:00 a.m. - 12:00 p.m.	Medical Staff Rounds Peter Bent Brigham Hospital
MONDAY, NOVEMBER 10	
*12:15-1:15 p.m.	Clinicopathological Conference Peter Bent Brigham Hospital
WEDNESDAY, NOVEMBER 12	
*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital)	Amphitheater, Peter Bent Brigham Hospital
*2:00-3:00 p.m.	Combined Clinic by the Medical, Surgical and Orthopedic Services Amphitheater, Children's Hospital

\*Open to the medical profession

OCTOBER-DECEMBER. Thirteenth Postgraduate Seminar in Neurology and Psychiatry Metropolitan State Hospital Page 348 issue of August 28.  
NOVEMBER 6 New England Hospital for Women and Children. Page 650, issue of October 23.  
NOVEMBER 10 Joint meeting of New England Society of Anesthesiologists and American Society of Anesthesiologists Incorporated. Page 530, issue of October 2.  
NOVEMBER 12 Division of Hospital Survey and Construction of the Massachusetts Department of Public Health Page 650, issue of October 23.  
NOVEMBER 13 Acute Myocardial Infarction Dr. William M. Chambers. Pentucket Association of Physicians 8:30 p.m. Haverhill.  
NOVEMBER 13-15 Association of Military Surgeons Annual Meeting Hotel Statler, Boston.  
DECEMBER 15-17 American Academy of Allergy Page 602 issue of October 16.  
FEBRUARY 6 American Board of Obstetrics and Gynecology Page 242 issue of August 14.  
MARCH 28-APRIL 4 American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.  
APRIL 19-23 American College of Physicians. Page xiii, issue of July 31.  
MAY 6-8 American Association for the Study of Goiter Page xiii, issue of July 31.  
MAY 11-15 American Association on Mental Deficiency Page 140 issue of July 24.  
MAY 17-20 American Urological Association Hotel Statler, Boston.

### DISTRICT MEDICAL SOCIETIES

FRANKLIN  
NOVEMBER 18  
JANUARY 13  
MARCH 9  
MAY 11 Annual Meeting Hotel Weldon  
All other meetings will be held at Franklin County Hospital

MIDDLESEX EAST  
NOVEMBER 19  
JANUARY 21  
MARCH 24  
MAY 12 Annual Meeting  
All meetings will be held at the Bear Hill Golf Club

NORFOLK  
NOVEMBER 25 Tufts Night  
JANUARY 27 Round-Table Discussion Bleeding from the alimentary tract  
FEBRUARY 24 Obstetric and Gynecologic Night  
MARCH 23 Harvard Night

PLYMOUTH  
NOVEMBER 20 Plymouth County Sanatorium, South Hanson  
JANUARY 15 Brockton Hospital, Brockton  
FEBRUARY 19 Toll House, Whitman  
MARCH 18 Goddard Hospital, Brockton  
APRIL 15 State Farm, Bridgewater  
MAY 20 Lakeville Sanatorium, Lakeville

SUFFOLK  
DECEMBER 4 Censors' Meeting

WORCESTER  
NOVEMBER 12 Grafton State Hospital  
DECEMBER 10 Worcester City Hospital  
JANUARY 14 St. Vincent's Hospital  
FEBRUARY 11 Worcester State Hospital  
MARCH 10 Memorial Hospital  
APRIL 14 Hahnemann Hospital  
MAY 12 Annual Meeting

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## AEROSOL THERAPY OF RESPIRATORY DISEASE

### A Report of Fifty Cases

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COLD SPRING HARBOR AND BROOKLYN, NEW YORK

**A**EROSOL therapy may be defined as the medicinal administration of fine solid particles or liquid mists as inhalants. The method has never been widely used in the treatment of disease, although asthmatic patients have been given symptomatic relief with epinephrine aerosols for many years. To anyone familiar with the basic studies on the subject,<sup>1-7</sup> the administration of antibiotics as aerosols appears to be a logical and necessary development. It may be anticipated that the advantages of simple administration and a relatively constant rate of absorption will eventually induce medical investigators to explore more fully the process of aerosolization as a technic for giving antibiotics, chemotherapeutic agents, enzymes, antibodies, endocrines, radiologically opaque solutions, bacteriophage, radioactive isotopes and many other diverse chemical materials.

From early in the war until recently, one of us (V B) was engaged in research‡ on the physical and biologic properties of aerosols for the Technical Division, Office of the Chief, Chemical Warfare Service. Publication in 1944 of a report on the production of penicillin aerosols and their inhalation by animals and man stimulated the interest of clinicians in the application of antibiotic mists for the treatment of pulmonary infection. Further studies were pursued for the Technical Division on a co-operative basis with the College of Physicians and Surgeons of Columbia University and later under contract to the Medical Division, Chemical Warfare Service. In addition, we have carried on an independent program resulting in the accumulation of clinical data on the use of aerosols in the treatment of respiratory infection. This work is reported below.

Considerable knowledge has been gained recently on the clinical application of penicillin aerosols,

notably by Olsen,<sup>10</sup> Barach et al,<sup>11</sup> Vermilye,<sup>12</sup> Segal and Ryder,<sup>13</sup> Humphrey and Joules<sup>14</sup> and by Southwell.<sup>15</sup> It is now known that blood levels well above the minimum bacteriostatic requirement to inhibit the growth of nonresistant staphylococci and streptococci can easily be obtained.<sup>11</sup> The presence of penicillin in the blood and urine after penicillin aerosol therapy may justifiably be regarded as proof that the antibiotic is being absorbed.<sup>9</sup> The attainment of high blood levels at the expense of unduly complex rebreathing apparatus and accessory equipment, however, does not seem to us a warranted procedure, except when demonstrably more effective clinically. Segal and Ryder<sup>13</sup> have obtained striking clinical improvement in 2 cases in which no blood level could be demonstrated after aerosol therapy. Their conclusions that blood levels are mainly of academic interest rather than practical value and that the clinical course of a disease should be the criterion of effective treatment are probably justified.

At the present time a trend to the use of increasingly complex accessory equipment in the production and administration of therapeutic aerosols is apparent.<sup>16-17</sup> The value of complex baffles, valves and rebreathing devices is problematical. Actually, all that is needed to administer aerosol therapy is a suitable nebulizer,§ a source of compressed air or oxygen and a rubber tube. Insertion of a Y tube or small hole in the tubing connecting the oxygen tank and nebulizer enables the patient to operate the nebulizer only during inhalation by placing his finger over the open end of the Y tube or hole in the rubber tube.<sup>11-13</sup> A small electrically motivated air compressor may be used as a substitute for tank oxygen, provided that the air is carefully filtered to remove any machine oil and that supplementary oxygen is not required.<sup>14</sup>

At the outset we were convinced that if penicillin aerosol therapy was to be a generally useful thera-

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‡This study was aided by a grant from the Josiah Macy Jr. Foundation.

§Vaponefrin—obtainable from Vaponefrin Company, Upper Darby, Pennsylvania—or DeVilbiss 40—obtainable from DeVilbiss Company, 111 Eighth Avenue, New York City.



peutic method, simplicity of equipment and procedure was vital. By means of a nebulizer (for which the ordinary unbaffled atomizer is not a substitute), the patient inhales aerosolized penicillin either through cannulae passing into the nose or by mouth, depending on the clinical problem involved. When possible, deep inspiration on the part of the patient aids in the maximum distribution and retention of aerosol. Our subsequent experience, as well as that of Olsen<sup>10</sup> at the Mayo Clinic, has demonstrated the value of a simple technic.

At the same time it is necessary to select the necessary minimum of equipment with care. Experimental evidence indicates that to penetrate to the smaller bronchioles and alveoli of the lungs, aerosols must be composed of small particles, on the order of magnitude of 5 microns in diameter or less.<sup>19</sup> Large particles are impinged by convection in the nose, throat and upper respiratory passages and are undesirable, except for the treatment of infectious tracheitis, laryngitis and other diseases of the larger respiratory passages or for mucosography.<sup>20</sup> Therefore, the clinician must distinguish between the ordinary commercial atomizer, which produces relatively large droplets on the principle of a flit gun, and the nebulizer. A nebulizer is constructed with some intermediate baffle interposed between the spray jet and the orifice, larger particles impinging on this baffle are broken into smaller droplets and expelled, or returned by gravitational force to the main reservoir for recirculation. Even some commercial nebulizers produce a considerable percentage of large particles, which merely means that a greater proportion of the inhaled solution is delivered to the surface of the throat, larynx and trachea. The treatment of respiratory disease may, in fact, be accomplished by an ordinary atomizer, as reported by Morse.<sup>21</sup> In this event the principal effect on alveolar or bronchiolar surfaces is achieved topically by the fraction of small particles present in an atomized spray, together with an indirect systemic action of material absorbed from epithelial surfaces of the upper respiratory tract. The method is suitable for nontoxic substances, but if Promin<sup>22, 23</sup> or similar materials are to be used further for topical aerosol therapy of the lower respiratory system, the spraying of atomized solutions is contraindicated as producing physically heterogeneous aerosols, a large component of which would contribute to systemic toxicity without reaching the alveolar surfaces. If it is desired to confine therapy predominantly to the bronchioles and alveoli, the clinician should ascertain that the nebulizer of his choice produces with 5 per cent glycerin a fine smoke that floats in the air, rather than a spray capable of wetting objects placed a few inches from the orifice. A convenient test is to direct the nebulizer at a pane of glass adequately warmed to prevent undue condensation. Physical analysis of aerosols

produced with nebulizers considered clinically efficient for treating pulmonary disease reveals a modal particle diameter of 1 or 2 microns. Particles of this size will reach the peripheral respiratory branches.

Inhalation of aerosolized penicillin is a form of topical application. Florey and Fleming at an early date emphasized the importance of the topical use of penicillin whenever possible, a point reiterated by Florey at the Twenty-First Clinical Congress of the Connecticut State Medical Society in September, 1946. In other reports the topical administration of high concentrations of penicillin combined with the anionic detergent, Aerosol OT (dioctyl ester of sodium sulfosuccinate), in the successful treatment of chronic osteomyelitis is described.<sup>24-26</sup> In the present study 34 subjects were treated with aerosols of the cationic detergent Zephiran (alkyl dimethyl benzyl ammonium chlorides in aqueous solution), employed as a solvent for antibiotics. In the treatment of any chronic disease, whether pulmonary infection or osteomyelitis, the existence of infective foci sheltered from the effects of routinely administered penicillin by fibrosis, purulent matter or avascularity is a serious problem. The local use of antibiotic solutions in combination with detergents whose pharmacology and toxicity have been studied<sup>27, 28</sup> is based on the following primary considerations:

Antibiotics administered in detergent solutions may possess the obvious advantages associated with detergency emulsifying properties and reduced surface tension. The breaking up of pus and cellular detritus in solutions of wetting agents has been shown by Palitz and Herman.<sup>29</sup> Detergents are employed in the treatment of empyema, ulcers and infected fractures and routinely for the disinfection of skin and mucous membranes. In the aerosol treatment of fibrosed and purulent areas of the respiratory tract by antibiotics it is evident that any substance that might increase the probability of effective bacteriostatic contact between micro-organism and the antibiotic is a desirable adjuvant.

The activity of both penicillin and streptomycin *in vitro* is synergistically enhanced by the presence of detergents. In fact, it has long been known that detergents may enhance the action of bactericidal and bacteriostatic agents generally.<sup>30</sup> Excluding detergents, we have observed a definite synergism of penicillin with 9-amino acridine hydrochloride and streptomycin, using *Staphylococcus aureus* among other test organisms. The wetting agents Aerosol OT and Zephiran Chloride also potentiate the activity of penicillin *in vitro*, although the effect is reduced in the presence of blood.<sup>31</sup> The activity of Zephiran with penicillin on *Staph. aureus* (strain 313, N R R L) is shown in Table 1. Viable organisms

were determined by dilution platings of samples taken from tryptose phosphate broth at one, six and twenty-four hours of growth at 37°C.

It is observed that in the presence of a combination of Zephiran and penicillin (at concentrations singly ineffective in checking the growth of *Staph aureus*) the surviving bacteria have been reduced in number to less than 0.1 per cent (Table 1). In solid mediums the same concentration of Zephiran uncombined with penicillin reduces surviving bacteria to  $2.5 \times 10^4$  per million (Zephiran, 1,700,000). A level of penicillin is chosen that reduces survivors to  $10^4$  per million (penicillin, 0.01 units per cubic centimeter). In

resistant organisms serve to complicate the problem of treatment and become a potential source of new infections that are resistant from the onset. Therefore, in all use of antibiotics in which selection to resistance may occur, it is most urgent to use a dose that will be effectively bacteriostatic for all organisms, including any that may have mutated to the initial step in the development of resistance. Antibiotics should be administered in large doses and with sufficient frequency to maintain bacteriostasis for the more resistant members of a heterogeneous bacterial population. When possible, local therapy should be instituted. The problem of drug fastness, of

TABLE 1 *Consecutive Assays of Staph. aureus from Tryptose Phosphate Broth Containing Penicillin and Zephiran Singly and in Combination*

ASSAY TIME hr	TUBE No	CONTENTS	BACTERIA PRESENT per cc
1	1	Zephiran (1,700,000)	$6.8 \times 10^4$
	2	Penicillin (0.035 units per cubic centimeter)	$9.3 \times 10^4$
	3	Zephiran (1,700,000); penicillin (0.035 units per cubic centimeter)	$6.0 \times 10^4$
	4	Control	$8.5 \times 10^4$
6	1	Zephiran (1,700,000)	$8.3 \times 10^4$
	2	Penicillin (0.035 units per cubic centimeter)	$1.6 \times 10^4$
	3	Zephiran (1,700,000); penicillin (0.035 units per cubic centimeter)	$2.7 \times 10^4$
	4	Control	$1.0 \times 10^4$
24	1	Zephiran (1,700,000)	$1.0 \times 10^4$
	2	Penicillin (0.035 units per cubic centimeter)	$8.4 \times 10^4$
	3	Zephiran (1,700,000); penicillin (0.035 units per cubic centimeter)	$6.1 \times 10^4$
	4	Control	$4.3 \times 10^4$

penicillin-detergent combinations there are no survivors among  $6.4 \times 10^4$  seeded bacteria.

Although an undeniable gap exists between clinical results and animal experimentation it is perhaps significant that in investigations conducted for the Medical Division, Chemical Warfare Service, it was observed that the administration of penicillin and Zephiran aerosols to mice with experimental pulmonary disease results in a reduction of mortality compared with penicillin aerosol controls.

Antibiotic-detergent therapy, like multiple chemotherapy generally, may be instrumental in reducing the incidence of refractory drug-fast infection incurred during the course of treatment. Our colleague, Demerec,<sup>22</sup> has shown that among staphylococci (and presumably among most other ordinarily susceptible bacteria) penicillin resistance occurs spontaneously in the absence of penicillin by a process of mutation among a certain proportion of penicillin-susceptible organisms undergoing multiplication. The same considerations apply to streptomycin.<sup>23</sup> We believe that the insidious appearance of resistant bacterial strains during a therapeutic program may be assumed to depend on a process of artificial selection *in vivo*. This involves the elimination of susceptible bacteria and the survival of their more hardy mutant descendants to form an ensuing generation of resistant pathogens. Surviving as a result of inadequate therapy, these

debated significance in clinical treatment with penicillin, appears destined to be of greater importance with increased use of streptomycin.<sup>24, 25</sup> On a genetic basis the likelihood that resistance will be developed by a micro-organism against two bacteriostatic agents used simultaneously is very small, being the product of two arithmetic fractions. These fractions represent the probability of resistance (mutation) occurring to protect the organism from either substance alone. If the interesting observations of Carpenter et al.<sup>26</sup> and our own studies on synergism can be interpreted in this manner, the use of multiple chemotherapy takes on particular significance and may prove to become an urgent necessity in the use of agents that depend on subtle metabolic mechanisms for their activity.

We are well aware that the use of antibiotic aerosols, particularly in combination with synergistic agents, is largely unexplored. The germicidal effects of wetting agents may be partially nullified by foreign materials<sup>21, 27</sup> or by variation in hydrogen ion concentration.<sup>28</sup> For this reason the principles expressed must be regarded primarily as working hypotheses. Our own clinical experience over a period of two years in the treatment of osteomyelitis and respiratory disease, however, leads us to believe that consideration of the accumulated case histories previously reported and presented below may lead to a wider clinical employment of multiple chemo-

TABLE 2 Summary of Cases of Bronchiectasis, Bronchitis, Sinusitis and Miscellaneous Infections Treated with Penicillin Aerosol \*

	DIAGNOSIS	DURATION OF TREATMENT da.	TREATMENT	DURATION OF ILLNESS	ORGANISMS RECOVERED	COMMENT
	Bronchiectasis	18	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	Since childhood	Nonhemolytic <i>Staph aureus</i>	No improvement after follow up in 1 yr no 2nd-yr follow-up available
	Chronic bronchiectasis with lung abscess, secondary to pneumonia	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	14 yr	Beta-hemolytic streptococcus and hemolytic <i>Staph aureus</i>	Patient shows marked improvement, particularly in this year, when given larger dosage
	Chronic bronchitis, with hemoptysis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	4 yr	No cultures	Patient seen in October, 1946, and showed evidence of parenchymal damage
M	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	1 yr	<i>Escherichia coli</i>	Marked improvement, expectoration diminished from 180 to 4 cc per day
F	Post-virus pneumonia, questionable Boeck sarcoid with diffuse nodule infiltration	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	5 yr	<i>Staph aureus</i> predominantly, <i>Esch coli</i>	Marked improvement, recent severe cold cleared up with routine bed rest no excessive expectoration
F	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	6 wk	<i>Esch coli</i> , beta-hemolytic streptococcus, hemolytic <i>Staph aureus</i> and <i>Mentha albicans</i>	Patient, graduate nurse who stated that she had contracted virus pneumonia from patient, was acutely ill and responded satisfactorily
7	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	3 yr	<i>Bacillus subtilis</i> and hemolytic <i>Staph albus</i> in sinus drainage, <i>Staph albus</i> , predominantly, in sputum	Complete recovery when seen in June, 1946, headaches associated with chronic sinusitis had entirely disappeared
8	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	10 yr	Hemolytic <i>Staph albus</i> and <i>B subtilis</i>	Patient made good recovery and has no symptoms at present
9	Acute exacerbation of chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	8 yr	Nonhemolytic staphylococcus	Excellent result, prior to aerosolization patient had many operative procedures for sinus drainage, swelling in eyes entirely subsided
10	Chronic bronchitis, with bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	4 yr	Alpha-hemolytic streptococcus (viridans group)	Patient has made excellent improvement to date, but follow up inadequate owing to brevity of time since treatment
11	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	20 yr	Nonhemolytic <i>Staph albus</i> in sinus drainage	Improvement to date excellent, but 2 months' follow-up too limited for final opinion
12	Chronic bronchiectasis, with emphysema	10	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	15 yr	Beta-hemolytic and alpha-hemolytic streptococcus, staphylococcus, <i>Esch coli</i> and <i>Pseudomonas aeruginosa</i>	Patient unimproved
13	Bronchiectasis	10	50,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	10 yr	Nonhemolytic <i>Staph aureus</i> , non-hemolytic <i>Staph albus</i> and <i>Klebsiella pneumoniae</i> (Type B)	Temporary improvement following treatment, patient now has recurrence and has been advised to have streptomycin treatment in view of gram-negative organisms
14	Chronic diffuse bronchiectasis, with healed tuberculosis	6	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	11 yr	Hemolytic <i>Staph aureus</i> , hemolytic streptococcus, <i>M. albicans</i> and <i>K. pneumoniae</i> predominantly	Patient unimproved
15	Bronchiectasis	5	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	Since childhood	Beta-hemolytic streptococcus, hemolytic <i>Staph aureus</i> and alpha-hemolytic streptococcus	Temporary improvement immediately after treatment Follow-up later revealed patient unimproved
16	Chronic diffuse pneumonitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	5 mo.	Beta-hemolytic streptococcus, non-hemolytic <i>Staph aureus</i> predominantly	Patient seen in October, 1946, and was unimproved
17	Chronic sinusitis with bronchial asthma	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	Since childhood	Alpha-hemolytic streptococcus and <i>M. albicans</i> hemolytic <i>Staph aureus</i> beta-hemolytic streptococcus and <i>Esch coli</i>	Marked improvement. Patient recently had upper respiratory cold, but no recurrence of the asthma
18	Bronchiectasis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	10 yr	<i>Staph albus</i> beta-hemolytic streptococcus predominantly heavy growth of <i>Esch coli</i> negative for gram positive cocci	Patient made good improvement. His breathing was greatly helped by reducing infection and increasing vital capacity
19	Bronchiectasis questionable Boeck sarcoid	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	2 yr	Alpha-hemolytic streptococcus	Patient has improved, but has changed residence from New York to Arizona which may be responsible for continued improvement
20	Bronchiectasis with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr	15 yr	Nonhemolytic <i>Staph albus</i> and hemolytic <i>Staph aureus</i> streptococcus predominantly	Patient showed immediate improvement but later had recurrence (one year) Recent attempts to follow up of no avail

TABLE 2 (Continued)

CASE No.	AGE	SEX	DIAGNOSIS	DURATION OF TREATMENT	TREATMENT	DATE OF ILLNESS	ORGANISMS RECOVERED	COMMENT
21	45	M	Chronic bronchitis, with anthracis attacks	46	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr	1 mo.	<i>E. coli</i>	Patient made immediate improvement. Recent follow-up cannot be obtained.
22	59	F	Chronic bronchitis, with anthracis	7	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr	1 yr	Fungi resembling <i>M. abscessus</i> ; nonhemolytic streptococcus predominately (gamma type)	Slight temporary improvement immediately after hospital discharge. No permanent improvement.
23	44	M	Chronic bronchitis, with sinusitis	14	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 24 hr	14 yr	Alpha hemolytic streptococcus predominately; few colonies of alpha hemolytic streptococcus; few colonies of slightly hemolytic <i>Staph. aureus</i> ; <i>B. subtilis</i> ; <i>M. abscessus</i>	Patient made immediate improvement. Recent follow-up cannot be obtained.
24	51	M	Chronic sinusitis, with diffuse bilateral bronchitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 24 hr	29 yr	Predominantly <i>Staph. aureus</i> ; hemolytic and nonhemolytic	Moderate improvement, but follow-up showed need for supplementary treatment. Now this patient a physician.
25	45	F	Chronic sinusitis	10	200,000 units of aerosolized penicillin dissolved in physiologic saline solution every 8 hr	6 mo.	Alpha-hemolytic streptococcus; predominately alpha hemolytic streptococcus; several colonies of hemolytic <i>Staph. aureus</i> and several colonies of <i>E. coli</i>	Follow-up one year after treatment indicates good improvement maintained.
26	72	M	Chronic bronchitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	Since childhood	Hemolytic streptococcus; <i>Staph. aureus</i> predominately	Result unsatisfactory, probably owing to diffuse pneumonia with clumps as result of submergent accident in childhood.
27	57	M	Chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr	14 yr	<i>Staph. aureus</i> ; predominately and fungi in sinus drainage; <i>E. coli</i> ; predominately in several colonies of alpha hemolytic and few beta hemolytic streptococcus.	Immediate improvement, but follow-up showed some recurrence overall benefit derived however.
28	51	F	Chronic bronchitis, with recurrent sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	10 yr	Nonhemolytic streptococcus; some <i>Staph. aureus</i> and <i>E. coli</i>	Patient has not benefited by therapy; in fact she considers herself more susceptible to colds since treatment.
29	22	M	Cold and productive cough	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	1 1/2 yr	<i>E. coli</i> ; predominantly few nonhemolytic streptococci and <i>Staph. aureus</i>	Result excellent until patient contracted cold, when condition worsened, however.
30	67	M	Chronic bronchitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	3 yr	<i>Staph. aureus</i> ; fungi resembling <i>M. abscessus</i> ; beta hemolytic streptococcus predominately	Temporary improvement; last report in December, 1946, indicated improvement not permanent.
31	45	M	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	1 1/2 yr	<i>Staph. aureus</i> ; predominately some alpha hemolytic and beta hemolytic streptococcus and	Good result; patient states that there is great improvement with little or no expectation.
32	37	M	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr	15 yr	Nonhemolytic streptococcus and <i>Staph. aureus</i>	Good result; patient originally referred for treatment of sinusitis; we did not endeavor plan and penicillin by nasal route helped recovery.
33	60	M	Chronic bronchitis, with chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	4 yr	<i>Staph. aureus</i> in sinus drainage; some nonhemolytic streptococci and some <i>Staph. aureus</i>	Moderate improvement maintained since April 1946.
34	57	F	Chronic bronchitis	10	60,000 units of aerosolized penicillin dissolved in physiologic saline solution every 12 hr	6 mo.	Few nonhemolytic streptococci; hemolytic <i>Staph. aureus</i> predominately	Patient made excellent improvement and states that she now has no expectoration.
35	44	M	Bronchitis, with massive enlargement of lung	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	15 yr	Hemolytic <i>Staph. aureus</i> ; <i>St. viridans</i> and <i>Staph. aureus</i> fungi	Very satisfactory result; patient has had no hemorrhages and a minimum of expectoration.
36	66	M	Chronic bronchitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	25 yr	Alpha hemolytic streptococcus; predominately nonhemolytic streptococcus resembling <i>M. abscessus</i>	Moderate improvement, but result not entirely satisfactory.
37	42	F	Bronchitis, with massive enlargement of lung	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	10 yr	Nonhemolytic streptococcus; <i>Staph. aureus</i>	Excellent improvement which has been maintained since October, 1946.
38	60	F	Bronchitis, with hemoptysis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	40 yr	<i>Staph. aureus</i> ; nonhemolytic streptococcus.	After many years of treatment elsewhere patient made remarkable recovery with penicillin by nasal route.
39	45	F	Acute exacerbation of chronic sinusitis	10	100,000 units of aerosolized penicillin dissolved in Zephiran chloride every 8 hr	3 yr	Nonhemolytic <i>Staph. aureus</i>	Very satisfactory result obtained with penicillin by nasal route.

Supplementary parenteral treatment was given in each case as described above.

therapy and to a reconsideration of the topical treatment of infection, both with benefit to the patient. All material accumulated over a period of two and a half years is reported. Follow-up reports have been established in all these cases.

### METHOD

Our original technic was to give the patient 50,000 units intramuscularly on admission to the hospital and to follow this with 10,000 every three hours for ten days. In many cases, to avoid unnecessary injections, we gave 50,000 units every twelve hours in Pendil for the required ten days. Intramuscular penicillin serves to supplement penicillin aerosol. Recently, to diminish the discomfort of frequent intramuscular injections, we have been giving 300,000 units of penicillin in 1 cc of beeswax and peanut oil every twenty-four hours, since Romansky and Rittman<sup>39</sup> have demonstrated that an assayable blood level may thus be maintained for about one day. In subsequent discussions of the value of aerosol therapy, the possible therapeutic contributions of parenterally administered antibiotics are implied.

In preparation for aerosol therapy we now use 0.5 cc of a 0.25 per cent solution of Neo-Synephrine in the nebulizer. This the patient deeply inhales before starting the treatment with penicillin. Neo-Synephrine is immediately followed by deep inhalation of 100,000 units of penicillin dissolved in 3 cc of Zephiran in a 1:1000 aqueous solution every eight hours. The patient is carefully instructed concerning the basic anatomic and physiologic principles involved so that he will use forced expiration and then deeply inhale to the full limit of his vital capacity, simultaneously breathing in the aerosolized penicillin with the detergent. Emphasis on this important phase of the therapy is vital if the topical principle is to be fully exploited. The patient is instructed to prolong inhalation one or two hours by resting between each inhalation. When finished, to utilize more fully the penicillin that is retained on the walls of the glass nebulizer, 1 cc of physiologic saline solution introduced into the same nebulizer is inhaled. This procedure is followed every eight hours for ten days. All patients have been hospitalized during the interval of treatment. In the hospital we were able to obtain the necessary bacterial cultures and to correct minor difficulties in technic. From the onset we were desirous of maintaining an adequate dosage of penicillin for a prolonged period so that the artificial selection of penicillin-resistant organisms, as described by Rammelkamp and Maxon,<sup>40</sup> could be avoided. In 4 cases, urticarial swelling and itching followed the administration of penicillin by inhalation.

### TREATMENT OF CHRONIC SINUSITIS, TRACHEOBRONCHITIS AND BRONCHIECTASIS

Chronic tracheobronchitis, often associated with bronchiectasis, pulmonary emphysema and sinusitis,

has been the most frequent type of respiratory infection for which we have found penicillin aerosol to be of aid. The sulfonamides have been administered in aerosol form in the treatment of bronchiectasis by Stacey.<sup>41</sup> Olsen<sup>10</sup> has given penicillin aerosol to 7 patients hospitalized for pulmonary resection, stating that the method is the best available to prevent complications following complete or partial lobectomy for pulmonary suppurative disease. Among 8 cases of bilateral or inoperable bronchiectasis, Olsen reports immediate improvement in 7 with thinning and reduction of sputum, but with some later remissions. Segal and Ryder<sup>13</sup> suggest that periodic retreatment with aerosols may be necessary in the proper management of inoperable bronchiectasis. Barach<sup>11</sup> states that no improvement occurred in 3 of 7 cases of bronchiectasis associated with other bronchial or pulmonary infection, and of 4 improved patients remission was later evident in 2. Barach administered 100,000 to 200,000 units of penicillin as aerosol over a period of five to thirty-five days. Bobrowitz et al.<sup>42</sup> have also noted a tendency for remission to occur after treatment of bronchiectasis with intramuscular injections, intratracheal instillation and aerosolization of penicillin. The complete fibrotic reorganization and irreversible functional damage resulting from chronic bronchiectasis and bronchiolectasis make it probable that repeated bacterial infection follows the most thorough and effective therapeutic program. In the evaluation of improvement, allowance must be made for the usual seasonal fluctuations in cough, and no amelioration may be regarded as permanent without prolonged and possibly lifelong observation.

A chronic syndrome of sinusitis associated with either bronchitis or bronchiectasis is frequent (Table 2). Upper respiratory infection has been treated as a general problem with aerosolized and supplementary intramuscular penicillin. More recently, Zephiran in a 1:1000 solution has been used as a solvent for penicillin, to be given as an aerosol. The resulting turbid suspension forms a stable mist.

Among 21 patients with bronchiectasis treated by penicillin aerosol therapy, adequate subsequent observations extending up to two years have been obtained. Of these, 5 were not helped, 6 improved temporarily but relapsed, and 10 were definitely benefited. A possible contribution to improvement was temporary hemidiaphragmatic paralysis produced by crushing of the phrenic nerve in 2 of the improved patients, both of whom had experienced hemorrhage and hemoptysis. In the group with bronchitis, 1 patient was not relieved, 1 relapsed after temporary disappearance of symptoms, and 8 showed improvement. In addition, a patient with bronchitis was aided, but in this case the observation period since treatment extended only for two months. Aerosol treatment of sinusitis may be quite effective, and suitable instruments with affixed

nasal catheters may now be obtained \* Sixteen persons with sinusitis either singly or in combination with other respiratory ailments received penicillin in physiologic saline solution or Zephiran as an aerosol Recent histories are available for 13 patients, of whom 10 showed clinical improvement with no relapse

#### DIFFUSE PULMONARY FIBROSIS WITH LIMITED VITAL CAPACITY

Pneumoconiosis caused by prolonged exposure to silicon dust and characterized by nodular fibrosis and emphysema has been recognized as an occupational disease for many years <sup>42</sup> Even when the proportion of inhaled silicon dioxide is relatively lower, as in certain coal-mining activities, a diffuse perilymphatic fibrosis is often associated with anthracosis The resultant dyspnea may be a severe physical handicap

It is now realized that the proper control of occupational pneumoconiosis should be prophylactic Yet persons engaged in mining activities before adequate protection had been made to prevent irreversible fibrotic damage to the lung present a serious and tragic problem Any therapeutic agent that will help this group with reduced vital capacity demands consideration by physicians engaged in industrial medicine Treatment with penicillin aerosol has been found to be of definite benefit in decreasing the respiratory deficiency noted in diffuse pulmonary fibrosis of occupational origin The following brief abstracts of case reports are of interest.

**CASE 40** A 68-year-old man with extensive fibrosis of both lungs had worked for many years in a granite quarry any activity produced marked dyspnea Examination disclosed many rales in the chest Aerosolized penicillin was given in October, 1944 producing great relief from the dyspnea A cerebral accident, with hemiplegia recently occurred and the patient is now in a county hospital Dyspnea presents no problem at present

**CASE 41** A 56-year-old man who had been a coal miner most of his life had considerable dyspnea in April 1945, with limited activities as a doorman Aerosolized penicillin was given in April, 1945 and the patient has carried on all his duties with no discomfort At present he has been urged to return for a yearly repetition of treatment but refuses because he has no symptoms and feels in good health

Since the vital capacity lost as a result of pulmonary fibrosis cannot be replaced, the cause of clinical improvement subsequent to the use of penicillin aerosol in pneumoconiosis is obscure The marked and unexpected regression in symptoms of dyspnea may have been due to a reduction in associated infection, with a resultant increase in vital capacity By all clinical signs, both patients have been greatly helped Physicians in mining areas confronted with the problem of silicosis and anthracosis are urged to investigate and report on a larger series of such

cases in which penicillin aerosol has been used The cases discussed above are insufficient to permit any categorical conclusions

#### SEVERE ASTHMA

The treatment of infective intrinsic asthma by penicillin aerosols has been reported by Barach<sup>11</sup> and by Segal and Ryder<sup>12</sup> Barach summarizes the result of his favorable experience, stating that of 4 patients relieved of asthmatic symptoms for one or two months but with subsequent remission, 2 were successfully treated by a second course of aerosol therapy Since most asthma is extrinsic in origin it is essential that a careful diagnosis be made to determine the etiologic role of bacteria before a program of penicillin aerosols is begun

Segal and Ryder<sup>12</sup> described no marked change in bronchospasm following penicillin aerosol therapy administered to 6 asthmatic patients The excellent result obtained in the following case may have depended in part on the use of a germicidal detergent (Zephiran in a 1:1000 aqueous solution) as a solvent for the penicillin

**CASE 42.** A 16-year-old boy with a history of severe infective intrinsic asthma for 8 years, which had been getting progressively worse, could not play or move about with companions At present, 18 months after the administration of aerosolized penicillin he has had only one attack and is able to carry on all normal activities for his age with no discomfort In November, 1946, he was seized with an upper respiratory infection and 48 hours later he had an asthmatic attack He was immediately hospitalized and aerosol therapy instituted with penicillin and streptomycin each for five days The patient responded satisfactorily and now has no symptoms

Prevailing opinions on the value of asthma penicillin aerosols in the treatment of asthma are contradictory and will presumably remain so, in view of the complex physiologic nature of the disease Asthma should properly be considered a symptomatic response to a wide variety of conditions, including allergic, toxic and psychogenic factors therefore, it does not appear probable that treatment of associated infection will always be successful Yet, in our opinion, and that of Barach,<sup>11</sup> aerosol therapy may be a satisfactory method of treatment if justified by bacteriologic studies

#### PUTRID LUNG ABSCESS

In 1942 Maier and Grace<sup>43</sup> reported the distinct clinical entity of putrid empyema, recommending treatment through surgical drainage by open thoracotomy Confirmation was afforded the previous observation of Neuhof and Hirshfeld<sup>44</sup> on the anaerobic nature of the causative micro-organisms Infection with anaerobic streptococci and staphylococci, mixed with spirochetes and aerophilic bacteria, has been described not only in putrid empyema but also in putrid lung abscess Since putrid empyema develops most frequently from the intrapleural rup-

\*DeVilbiss 640 obtainable from DeVilbiss Company 111 E 84th Avenue New York City

ture of bronchiectatic or abscessed regions of the lung, particular interest is attached to the adequate control of these contributory diseases. The aim of medicine should be preventive rather than remedial.

In the following case, aerosolized penicillin in Zephiran, supplemented by parenteral penicillin, was successful in curing a putrid lung abscess without surgical interference.

**CASE 43** This patient gave a history of so-called "pneumonia" for 3 weeks, which had been getting progressively worse, with expectoration of  $\frac{1}{2}$  to 1 cupful of foul, putrid sputum a day and a daily temperature of 103°F. X-ray study showed a large lung abscess in the right upper lobe. Penicillin was given parenterally, with penicillin in Zephiran aerosol (for 10 days), and the patient promptly made an uneventful recovery. At follow-up study 3 months later, there were no symptoms. X-ray examination showed complete resolution of the abscess.

The topical administration of penicillin-detergent solutions may ultimately prove to be of aid in the elimination of gram-negative bacilli and penicillinase-producing bacteria symbiotically involved in putrid lung abscess and ordinarily unchecked by penicillin alone. It is essential that a detergent capable of acting in high dilution, whose antibacterial properties have been studied, be utilized. At the same time, a conservative distinction must be drawn between the accepted germicidal potentialities of detergents in vitro and their largely undetermined value as inhalational aerosols. Without undue optimism it is believed that the prompt and judicious use of aerosol therapy will, on occasion, prevent the desperate clinical picture of advanced anaerobic infection. When surgery is indicated for pulmonary disease, preoperative treatment with aerosols should be of value, according to the principles elaborated by Olsen.<sup>10</sup>

#### ACTIVE PULMONARY TUBERCULOSIS

Since the tubercle bacillus is not sensitive to penicillin concentrations ordinarily attainable, it is at once evident that penicillin aerosol does not afford the promise of streptomycin in the treatment of tuberculosis. It is well known, however, that a considerable degree of damage in tuberculosis of the lungs is caused by associated bacteria, notably staphylococci and streptococci. If these secondary invaders could be controlled by penicillin, it was thought that a possible resultant reduction in bacterial flora and general toxemia might provide an opportunity for the natural defenses of the body to effect an arrest or regression of the disease.

The following are brief abstracts of cases treated for secondary infection with penicillin aerosol.

**CASE 44** This 26-year-old patient had pulmonary tuberculosis of the left upper lobe, with multiple cavities, positive sputum and a high sedimentation rate (77 mm in 1 hour by the Westergren method). The phrenic nerve was crushed, and hemidiaphragmatic paralysis was done, with aerosol therapy as described above. The patient was not helped.

**CASE 45** This 34-year-old patient gave a history of tuberculosis of the right upper lobe of 10 years' duration. The

sputum was positive. Frequent rest and artificial pneumothorax had been unsatisfactory, aerosolized penicillin was not helpful, but was regarded as an important preoperative aid to a two-stage thoracoplasty. The sputum was negative for a period, and the patient actively engaged in business. The treatment was perhaps instrumental in changing a case of acute pulmonary tuberculosis to a chronic one by control of the secondary infection in the lung and diminishing of systemic toxemia. A preliminary phrenic-nerve operation had been done. The possibility that temporary improvement would have occurred spontaneously without treatment cannot be ruled out. Four months after discontinuation of treatment a positive sputum and evidence of activity in the lung were found.

**CASE 46** This 44-year-old patient had bilateral pulmonary tuberculosis, with cavitation in the left lung. The sputum was positive, and the sedimentation rate was high. Aerosolized penicillin was not helpful.

**CASE 47** A 40-year-old woman had extensive bilateral pulmonary tuberculosis. There was a high sedimentation rate (78 mm in 1 hour). The sputum was positive. Aerosolized penicillin was used, but the vital capacity was so limited that the patient could not follow the prescribed technique of deep inhalation. This patient died four months later from pulmonary tuberculosis. The use of aerosolized penicillin was unsatisfactory.

These 4 patients with advanced tuberculosis were treated before streptomycin became available and were not benefited by efforts to control secondary bacterial invaders with aerosolized penicillin.

Streptomycin as an aerosol has been employed by Nichols and Herrell<sup>46</sup> and by Olsen<sup>47</sup> in the treatment of bronchiectasis with gram-negative involvement, and also by Hinshaw, Feldman and Pfuetz<sup>48</sup> in the therapy of tuberculosis. It is perhaps significant that streptomycin has been reported to be less diffusible in the body than penicillin—an observation indicating possible advantages in the topical treatment attainable by aerosolization. The use of streptomycin as an aerosol in the treatment of pulmonary tuberculosis appears, a priori, to be worthy of extensive investigation. We have had the opportunity to hear both Hinshaw and McDermott report their experiences in the therapy of tuberculosis with parenteral streptomycin. Since streptomycin as now administered appears in some cases to be merely a palliative,<sup>48</sup> a co-ordinated therapeutic program may be required, involving suppression of the tubercle bacillus and any secondary infection, together with adequate diet and rest for the patient. Efforts to increase liver efficiency may do a great deal to diminish damage by bacterial toxins. By aerosol therapy it may be possible to deliver streptomycin topically and in larger doses than can be placed in the lung by parenteral methods. One of us (E. J. G.) believes that thoracoplasty should not be done until the more conservative plan of therapy has been adequately tried. With a larger output of streptomycin gradually becoming available, a method of topically placing this antibiotic or other chemotherapeutic agents in more direct contact with tuberculous lesions in the lung might have a profound effect in limiting the magnitude of thoracic surgery required in the treatment of pulmonary tuberculosis and in altering the course of the disease.

In addition to the administration of aerosolized penicillin in Cases 44-47, a small series of patients were treated with streptomycin aerosol, the detergent Zephiran in a 1:1000 aqueous solution being used as a solvent. In the topical eradication of acid-fast bacteria isolated in fibrosed, calcified or caseous tubercles the potential significance of an acutely germicidal and detergent aerosol becomes obvious. Yet we do not at present know if the necessary level of germicidal and detergent efficiency can be reached without associated toxic and hemolytic effects. Our present clinical experience is too inadequate to justify report of more than the arrest of pulmonary tuberculosis with symptomatic improvements in 4 patients treated with streptomycin in Zephiran, 1 of whom (Case 49) received direct intrapleural instillation for bronchopleural fistula.

**CASE 48.** This 36-year-old patient stated that in 1934 a diagnosis of left pulmonary tuberculosis had been made. Artificial pneumothorax was given until 1938 when pleural fluid was aspirated and *Mycobacterium tuberculosis* was found. Subsequently the patient developed chronic tuberculous empyema that had drained constantly for 8 years and entered the Grace Clinic in 1941. All accepted methods of treatment, including complete thoracoplasty of the left side were used but empyema continued to drain. Biopsy of the visceral and parietal pleura showed a classic picture of tuberculosis. On October 14 and 15, 1946, a solution was made of 20 cc. of Zephiran chloride aqueous solution (1:1000) with 1 gm. of streptomycin and 5 cc. was injected directly into the pleural cavity every 5 hours for six doses. Five days later the chronic tuberculous sinus tract closed for the first time in 8 years and now, 1 year later, it is still closed. The clinical condition is now good.

**CASE 49.** A diagnosis of pulmonary tuberculosis in this 37-year-old woman was made in 1929. A continuous artificial pneumothorax was given. The patient, when 2 months pregnant, developed a bronchopleural fistula with a fluid level 9 cm. above the left leaf of the diaphragm. Empyema fluid drained into the fistula. There was a continuous cough. The patient spoke with difficulty. She appeared moribund when seen on November 14, 1946. The immediate problem was supportive treatment with control of the empyema and bronchopleural fistula of the left side. For the following 7 days 1 gm. of streptomycin dissolved in 10 cc. of 1:1000 aqueous solution of Zephiran was injected into the pleural space and 200,000 units of streptomycin and 100,000 units of penicillin were administered intramuscularly every 12 hours in becwax and peanut oil for 6 weeks. The patient gave birth prematurely on November 22, 1946. The baby died. The hacking cough and copious expectoration started to subside after the intrapleural instillation of streptomycin detergent and have now been eliminated. The fluid level was reduced to 3.7 cm. All clinical and laboratory data confirm the obvious symptomatic improvement. The seriousness of the illness may be gauged by the fact that the patient cannot recall anything that took place during the first ten days of her confinement to the hospital. Aerosolized penicillin therapy was attempted and stopped because of great distress to the patient, with some hemoptysis. The possibility of mediastinal shifting and flutter with consequent circulatory and respiratory embarrassment may preclude forced breathing of aerosols when bronchopleural fistula is present.

**CASE 50.** A 29-year-old patient was known to have had bilateral tuberculosis for 3 years. She entered the Grace Clinic on November 13, 1946 with a hydropneumothorax of the right side. Diffuse mottling and infiltration were noted throughout the left portion of the chest. On the right a temporary hemidiaphragmatic paralysis was accomplished by crushing of the right phrenic nerve. On December 20 the patient was given 100,000 units of penicillin and 200,000 units of streptomycin as aerosol in 3 cc. of a 1:1000 solution of Zephiran every 8 hours together with 200,000 units of streptomycin in becwax and peanut oil every 12 hours.

Penicillin streptomycin-detergent aerosol was continued for 3 weeks. Streptomycin given intramuscularly has been continued to date.

**CASE 51.** A 28-year-old woman had been seen at various intervals since March 7, 1945. She had no specific complaint except slight colds, with a minimal cough at various times, and fatigue. X-ray studies of the chest on six occasions from the first visit failed to establish any definite diagnosis. On October 30, 1946 the patient had an acute cold and cough. Routine x-ray study of the chest on that date was reported as showing a moderate infiltrative lesion involving the left apex. In the first interspace anteriorly there was a small cavity in this apical lesion. The patient was hospitalized immediately, and antibiotic therapy started. Penicillin and streptomycin were given with detergent Zephiran Chloride in a 1:1000 solution as an aerosol and also systemically in peanut oil. X-ray studies on January 2, 1947 revealed moderate fibrosis in the left apex. The cavity was no longer visible. There was no definite evidence of active infiltration at that time. The patient could take aerosolized streptomycin and penicillin for only 1 month but from the onset of therapy she had had 0.5 gm. of streptomycin daily. Treatment was begun on November 1, 1946, and is being continued to date. This patient has clinically made a satisfactory recovery as confirmed by x-ray examination, but in spite of the clinical improvement a high sedimentation rate (38 mm in 1 hour by the Westergren method) indicates the importance of not permitting clinical or x-ray data alone to determine the plan of a patient's activity.

Any attempt at present to judge the merit of the therapeutic programs outlined would be premature. Yet there can be no doubt that symptomatic improvement has occurred, and it is highly probable that death was imminent in Case 49 before treatment was instituted. Complete laboratory reports have been kept, and include findings of negative sputum after treatment. As a negative finding, however, the absence of *Myco tuberculosis* in the sputum is regarded as of doubtful diagnostic value. No vestibular disturbances have been reported by the patients. Although not properly within the scope of a paper on aerosols, Cases 48 and 49 have been included as examples of the local employment of antibiotic-detergent therapy, which assumes significance in the light of Hinshaw's findings. Hinshaw et al.<sup>48</sup> state that among 7 cases of tuberculous empyema treated with streptomycin routinely, definite improvement was noted in only 1. The refractory nature of tuberculous empyema is ascribed in part by these investigators to the granulomatous nature of the diseased pleura. The reduced surface tension of streptomycin detergent may afford a more efficient infiltration of superficial granulomatous processes.

One of us (E. J. G.) has had the opportunity to participate in surgical treatment of pulmonary tuberculosis during the last two decades, in county hospitals, private sanatoriums and private practice. During that period the radical surgical procedures advocated above have been employed. In the late follow-up study of patients treated by radical surgery it is tragically evident that surgical procedures are often far from ideal. It is now generally agreed that the accepted conservative procedure of bed rest, adequate diet and nursing care remains the method of choice in the treatment of tuberculosis. Anti-



biotic-detergent aerosol therapy should be regarded as a supplement to the conservative management of tuberculosis, an approach that should be thoroughly explored before resorting to surgery. Since others have reported the arrest of pulmonary tuberculosis with parenteral streptomycin,<sup>48</sup> any proper evaluation of topical streptomycin-detergent therapy must await the accumulated experience of careful observation over a long period.

### SUMMARY

The mechanical equipment necessary for effective aerosol therapy is preferably simple, consisting of a suitable nebulizer for oral inhalation and a nebulizer with attached cannulae for nasal inhalation. The distinction between atomizers and nebulizers should be understood by the physician. The medical use of aerosols demands a basic knowledge of the fundamental physical principles involved in the behavior of inspired particles of different sizes.

Aerosol therapy is considered a form of topical treatment. Topical administration of antibiotics in detergent solutions may provide the physical advantages associated with reduced surface tension and the antibacterial advantages contingent on synergism and the reduced likelihood of drug-fast infection.

Clinical experience of more than two years has shown antibiotic aerosol therapy to be a valuable supplement to parenteral treatment of respiratory disease, including intrinsic infectious asthma, bronchitis, bronchiectasis, sinusitis and, more recently, tuberculosis. Except in selected cases, aerosol therapy should be attempted before surgery is resorted to.

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## SERVICES OFFERED TO THE PHYSICIAN BY THE MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH\*

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BOSTON

IN 1850 Lemuel Shattuck, a representative in the General Court of Massachusetts and a bookseller in Concord, alarmed to find that so many persons died in the prime of life, presented the first sanitary survey, entitled "Report of a General Plan for the Promotion of Public and Personal Health," to the General Court. In 1869 the first state board of health in the country was established by the General Court in Massachusetts. This Board was authorized to take cognizance of the interest of health and life among the citizens of Massachusetts, and to make sanitary investigations and inquiries concerning the people, the causes of disease, especially of epidemics, the sources of mortality and the effects of localities, employments, conditions and circumstances on the public health, as well as to gather information regarding such matters as it may deem proper for diffusion among the people. In subsequent legislation, the Massachusetts Department of Public Health was given broad authority, which has continued to increase, and is now charged with the following responsibilities: to make investigations of the sale of drugs and food and adulterations thereof, to advise the government and others of sanitary conditions in public institutions, to have oversight of inland waters and sources of water supply, as well as vaccine institutions, and to produce and distribute antitoxin and vaccine lymph and such specific serums for protective inoculations, diagnosis or treatment against typhoid fever and other diseases as the Department may from time to time deem advisable, to make annual examinations of all main outlets of sewers and drainage of the towns of the Commonwealth, to define diseases dangerous to the public health, to investigate contagious diseases, to furnish remedies for ophthalmia neonatorum, and to make minimum isolation and quarantine regulations. Many other responsibilities too long to list in this presentation have been assigned to the Department of Health.

Passing through many vicissitudes of organization, the Board of Health eventually assumed its present form in 1914 as a department of public health with an advisory public-health council and a commissioner as the administrative executive officer. It now employs approximately eighteen hundred people and expends an annual budget of about \$8,000,000 derived from state, federal and private funds. The Department of Public Health has be-

come responsible not only for the preventive aspects of public health but also for the promotion of optimal health and for the administration of medical-care programs, it is also charged with the direction of five state institutions.

### ORGANIZATION

The Commissioner, appointed for a period of five years by the Governor, is charged with the administration of the laws relative to health and sanitation and the regulations of the Department. He is required by law to prepare rules and regulations for the consideration of the Public Health Council and to direct employees of the Department to assist in the study, suppression or prevention of diseases in any part of the Commonwealth. Annually, he must submit to the Council a report containing recommendations regarding health legislation. He is required to be a physician schooled in sanitary science and experienced in public-health administration. He is the executive and administrative head of the Department and acts *ex officio* as chairman of the Public Health Council.

The Public Health Council, consisting of the Commissioner and six other members, meets at least once a month. Members are appointed by the Governor, one each year for a term of six years. The Council is required to promulgate rules and regulations, take evidence in appeals, hold hearings and discharge its duties as required by law. Hearings may be held by the Commissioner or by a director of a division of the Department if so authorized by the Commissioner and Council.

### Divisional Organization

Because of the complex field activities, the Department is divided into the following sections: Administration, Biologic Laboratories, Cancer and Other Chronic Diseases, Communicable Diseases, Dental Health, Food and Drugs, Local Health Administration, Maternal and Child Health, Sanitary Engineering, Tuberculosis and Venereal Diseases.

**Administration.** This division, whose director is the Commissioner, is concerned primarily with the over-all administration of the Department, including physical and personnel matters, the development of rules and regulations, state and federal legislation, the dissemination of information through the Bureau of Health Information, the licensing of hospitals and the conduct of the Hospital and Health Center Survey and Plan, as authorized by Public Law 725, whereby Massachusetts is to receive a sum

\*Presented at the annual meeting of the Massachusetts Medical Society May 22, 1947.

†Commissioner, Massachusetts Department of Public Health.

of \$8,000,000 over a period of five years, provided it be matched by double this amount in local or state funds, for assistance in the construction of health centers and hospitals, which are included in a plan now being developed under the direction of a special commission appointed by the Governor. A survey of hospitals and public-health centers is being completed to determine the actual needs of the Commonwealth, and the formulated plan is to provide coverage to meet existing needs.

Through the efforts of the Bureau of Hospital Licensing, improvements have been made in hospital staff organization, hospital records, obstetric care and the management of nurseries for the newborn. The Division of Administration advises local boards of health, voluntary health associations and professional organizations and consults them regarding the administration of the Department. It acts as a co-ordinating or liaison group with other governmental departments. The Commissioner serves as a member of the Milk Regulation Board and the Rating Board, and, most important, he also serves as a member of the Massachusetts Approving Authority for Medical Schools. This last organization has been effective in raising the standards for medical practice in Massachusetts. The Department of Public Health receives advice and federal grants-in-aid from the United States Public Health Service and the Children's Bureau, both in the Federal Security Agency. These funds are received for the following purposes from the Public Health Service for venereal-disease control, tuberculosis control, general public health, industrial hygiene, cancer, hospital construction and survey, and from the Children's Bureau for maternal and child health, crippled-children's services and emergency maternal and infant care. Private funds are also expended for various specifically designated purposes.

**Dental Health.** This is the newest division of the Department and is primarily concerned with the promotion of dental-health education, the development of programs for the prevention of dental caries, the promotion of dental clinics for children and the dissemination of information relative to the care of teeth of children and adults. At present the Department is not conducting any service program except through well-child conference demonstrations in which dentists and dental hygienists make examinations and inspections of teeth for the information of parents, referring the children to the family dentists for treatment.

**Food and Drugs.** This division is truly the policeman of the Department and is primarily concerned with the sanitation and safety of foods and, secondly, with the purity of contents and the consumer value of foods and drugs. Inspections are made of all types of food-manufacturing establishments, including bakeries, slaughtering houses, poultry-slaughtering houses, pasteurization and other milk-handling concerns, wholesale and retail stores, cold-storage

plants, soft-drink manufacturers and other food-processing establishments and restaurants. In addition, samples of many foods and drugs, as well as filling material of mattresses and upholstered furniture, are collected for analysis for adulteration, misbranding or safety. This assures the consumer that he is buying what he thinks he is buying, and that the food that he consumes is not only nutritious but also safe and sanitary. Through the Division of Food and Drugs licenses are issued to manufacturers and wholesale distributors of narcotic drugs. Routine check-up examinations are made on pharmaceutical products, especially those liable to deterioration (such as vitamin B<sub>1</sub> and digitalis), and on the accuracy of druggists in filling prescriptions. Notification to physicians is made of products determined harmful or dangerous to use.

**Maternal and Child Health.** This division is responsible for the promotion of prenatal care, for the development of a program for the care of premature infants, for the institution of refresher courses for physicians, for the conduct of well-child conferences and for the promotion of both preschool and school health programs. It has developed the Massachusetts vision test, which has replaced the Snellen chart, and is now promoting audiometer testing of the hearing of the children. Audiometer testing is done in groups and checked on an individual basis. Children who have apparent visual or hearing defects are referred to physicians for follow-up study. This division is also responsible for the administration of the Crippled Children Services—a program that has been co-ordinated with the activities of the District Medical Societies. Consultants for the state clinics are available together with a corps of other specialists, such as physical therapists, nurses, medical social workers and nutritionists, to assist in the care of children who are referred by physicians or social agencies. Any child may obtain diagnostic services, but only children whose families cannot afford to pay for medical and hospital care are accepted for treatment. One of the war activities has been the Emergency Maternity and Infant Care Program, which is in the process of gradual liquidation. Under this program any woman who was eligible prior to June 30, 1947, may receive benefits for maternity care. This includes the payment of physicians in accordance with the fee schedules set up by the Children's Bureau, and hospital services in accordance with schedules for payment to hospitals on a cost basis. The number of maternal cases cared for under this program as of May 1, 1947, was 32,643, including 15,668 from September, 1943, to December 31, 1944, 10,072 in 1945, 6284 in 1946, and 619 from January 1 to May 1, 1947. Servicemen's children under one year of age are eligible for health supervision and pediatric care on a similar schedule of fees to physicians and a payment based on cost to hospitals. The total number of children as of May 1, 1947, was 9255, including 2521

from September, 1943, to December 31, 1944, 3117 in 1945, 2833 in 1946, and 784 from January 1 to May 1, 1947. The Division is particularly concerned with the development of a school health program in co-operation with the Department of Education and, it is hoped, the inauguration of a local school-physician consultant service for this purpose.

**Sanitary Engineering** One of the largest divisions of the Department is that of Sanitary Engineering, which is responsible for the supervision of water supplies, sewage disposal and drainage systems and for advice to cities, towns and persons on water supply and sewerage problems. All construction or reconstruction of these plants must be approved by the Department. An extensive laboratory for chemical and microscopical analysis of specimens of water and effluents of sewage-disposal systems is located in the State House and also at the Lawrence Experiment Station, where a bacteriologic laboratory is also maintained and where many systems now used throughout the country for the treatment of water, industrial wastes and domestic sewage have been developed.

This division is also responsible for the abatement of noisome trades, — that is, industries that may cause a nuisance because of odors, — for the control of pollution of streams, ponds and tidal waters, for the supervision and approval of areas for the taking of shellfish and for the operation of shellfish-purification plants and shellfish-handling establishments. This division is also responsible for the general over-all supervision of cross-connection between plumbing and sewage-disposal systems.

**Biologic Laboratories** The Division of Biologic Laboratories has more than doubled in size in the past two years. Its primary function has been the manufacture of prophylactic and therapeutic biologic products. The Massachusetts Department of Health was the first to make diphtheria antitoxin available for the treatment of diphtheria. We are now adding to our present products the manufacture of whooping-cough vaccine and hope to add tetanus toxoid in the near future. It is the Department's recommendation that every child three months to six months of age should be immunized against whooping cough, and those six months to nine months against diphtheria, and that whenever possible, tetanus toxoid be added in whatever combination with the above two that the physician may desire. The Department expects to manufacture all three products in various combinations for free distribution as soon as personnel becomes available. In addition, the child at about nine months should be vaccinated against smallpox. Ideally, if the family can afford the expense, a booster inoculation of whooping-cough vaccine should be given during the second year of life. Prior to entering school, every child should receive a booster dose of diphtheria and tetanus-toxoid combination and should be revaccinated against smallpox. The Department does not

manufacture influenza vaccine and does not recommend its routine use. Typhoid vaccine is now manufactured, and we expect soon to produce the triple typhoid-paratyphoid A and B vaccine for those who may wish its use. The employment of typhoid-paratyphoid vaccine should be limited to groups who are traveling abroad and should not be recommended as routine.

One of the newest activities of the Department is the furnishing of whole blood, plasma, gamma globulin and other fractions of whole blood free of charge to people in communities that have contributed blood on a voluntary basis to the State Blood Program. Because of the limited supply of blood, physicians are urged to select cases for the use of whole blood and blood fractions with care, so that these life-saving products will not be wasted. Supplies are made available first to the families of donors who have contributed during the past year and then to other people in the same community. In an emergency others may obtain these products but not routinely until their community has deposited with the State Blood Program a sufficient amount of blood to ensure that any calls they will make will not overdraw their account. Any physician desiring information regarding the use of any of the prophylactic or therapeutic products may call on the Division of Biologic Laboratories for consultation and advice. The Bacteriology Laboratory, previously located in the State House, and the Serology Laboratory, formerly located at Harvard Medical School, have recently moved to new quarters at 281 South Street, Jamaica Plain. Serology and Bacteriology Laboratories are now essentially merged in quarters adjacent to the Division of Biologic Laboratories.

**Tuberculosis and Sanatoria** This division is responsible for the administration of five hospitals and of our tuberculosis program in general. The tuberculosis program may be divided into three main categories. The first comprises diagnostic services, which are available to communities through the outpatient departments, fourteen consultation clinics and three mobile chest x-ray units. We are now making surveys of state institutions, industrial groups and certain selected communities. It is the objective of the Department to make a chest x-ray examination of every person over fourteen years of age within the next five to ten years to disclose active cases, which will be further confirmed by more detailed examinations. Cases that are found to be positive will be hospitalized in sanatoriums so as to afford the patients themselves a better and quicker chance of cure or arrest and to remove, if possible, the danger of infection of their own households and associates. The second aspect of the program has to do with the follow-up study of patients and contacts, including patients who have been discharged from institutions as arrested or against advice.

These must be followed to assure that they will receive the best possible care under the circumstances, that they do not break down, that they are pursuing an occupation that is not a hazard and that they are not a source of infection. The third phase of the tuberculosis program is that of sanatorium care. The Department pays a subsidy of \$5.00 per patient to county and municipal sanatoriums, provided they meet the established standards of the Department. At the present time all county and municipal sanatoriums are approved except the Lowell Isolation Hospital. The Department is responsible for the administration of the following institutions:

Rutland State Sanatorium, comprising 365 beds for the care of pulmonary tuberculosis. This was the first state tuberculosis hospital in the country. It should be rebuilt within the Greater Boston area, since it serves primarily the patients from the eastern part of the state.

North Reading State Sanatorium, with 240 beds, of which half are devoted to the care of tuberculosis of children and the other half will be devoted, as soon as personnel is available, to the care of acute rheumatic fever.

Lakeville State Sanatorium, with 304 beds, is devoted primarily to the care of extrapulmonary tuberculosis, such as that of the bones and joints and the kidneys. This institution also has special wards devoted to the care of patients with crippling conditions due to infantile paralysis and spastic paralysis. A limited number of acute cases are also received for hot-pack treatment.

Westfield State Sanatorium, with 189 beds for tuberculosis and 50 for cancer, receives cases of pulmonary tuberculosis and cancer and suspected cancer from the western part of the Commonwealth. A large outpatient department will receive any case referred to it either by a private physician or by a welfare organization.

Pondville Hospital, with 145 beds, was the first state cancer hospital established in the United States. A number of new buildings are needed to modernize the institution and to provide adequate living quarters for employees. Approximately six to seven thousand visits are made annually to the out-patient department.

Admission to these sanatoriums is through application made by the private physician and sent to the State House to the Division of Tuberculosis and Sanatoria. Anyone seeking advice about these institutions may call either the State House or the institutions directly.

**Communicable Diseases.** By law, the attending physician is required to report by name and address to the local board of health every case of disease declared dangerous to the public health. Boards of health furnish proper forms and may seek additional information. The Department of Public

Health issues minimum isolation and quarantine regulations, which are enforceable. Local boards of health may have more stringent regulations, but we do not recommend such additions. This division investigates all major cases of communicable diseases with the assistance of the district health officers as well as its own staff. In cases of outbreaks of serious nature, such as food-borne infection or infectious diarrhea of the newborn, a field unit is quickly organized and may call on the assistance of one of the medical schools or the Harvard School of Public Health. A diagnostic laboratory is available to which any physician may send specimens in kits provided by the Department.

This division is prepared to assist physicians in the diagnosis and treatment of more complicated cases of communicable disease. A list of consultants is available to determine the presence or absence of infantile paralysis. Consultants are not available, however, for cases in which paralysis is already present. A list of consultants is published annually in the *New England Journal of Medicine* or may be obtained from district health offices, from the local chapters of the National Foundation for Infantile Paralysis and from local boards of health.

The Division evaluates new immunization procedures, collects and analyzes morbidity and mortality data and issues periodic notices through the column of the Department in the *New England Journal of Medicine* of pertinent information on the incidence and prevalence of communicable diseases in the Commonwealth. Consultant and advisory service is available through its staff and that of our district health offices.

**Local Health Administration.** This is one of the newest as well as one of the largest divisions in the Department. In it are the bureaus of Public Health Nursing, Nutrition, Sanitary Inspection and Medical Social Work. This division supervises the work of the eight district health offices. The personnel of the district health offices are available as consultants and advisers to the medical and nursing profession and to the local boards of health. They are also available to physicians in the assistance and diagnosis of communicable diseases on problems pertaining to the handling of these cases in general hospitals or in homes. At the request or recommendation of the attending physician the Nursing Bureau of this division will provide nursing care for patients sick in the home, and the Nutrition Bureau will prepare special diets to assist individuals or families with nutrition problems. The Social Service Bureau will furnish information to an attending physician on numerous problems such as adoptions. This bureau also assists physicians in making arrangements for convalescent, nursing or terminal care of patients or for temporary care of children when the mother is hospitalized. District Health Officers have by law certain functions that they must perform, such as inspection of hospitals and other institutions,

the investigation of major cases of communicable diseases, the routine and semiannual check-up on typhoid carriers and the promotion of public health in all the communities of the Commonwealth.

**Veneral Diseases** The Division of Venereal Diseases subsidizes twenty-five clinics throughout the State with the co-operation of local boards of health and hospitals. Through these clinics penicillin is made available for the treatment of every case of gonorrhea, syphilis and other venereal diseases. Any patient who cannot afford private treatment may be treated, and transportation to these clinics is also afforded to those unable to pay. The present treatment consists of 2,400,000 units of penicillin over a period of seven and half days, with 0.2 gm. of bismuth subsalicylate given intramuscularly every other day for five doses. Cases of venereal diseases are at present not required to be reported by name. They are reported directly to the Department of Public Health by initial or number. Physicians may report by name if they so desire. Cases that lapse treatment must be reported by name and address for follow-up by workers who are made available through state funds to private physicians in clinics. The law requires that a person desiring to be married must have a serologic blood test performed in an approved laboratory. The Department of Public Health, through the Division of Communicable Diseases, approves laboratories for serologic tests. Persons who have positive tests may marry, but the physician is obliged to inform both parties of the positive reaction and should report the patient to the Department. Physicians are further required to make an examination of the blood of all pregnant women. All specimens may be sent to the Department of Public Health or to approved laboratories. A list of approved laboratories may be obtained from the State House or from the district health offices.

The Department is now experimenting in the treatment of syphilis with penicillin in peanut oil and beeswax. Daily injections of 300,000 units over a period of eight or nine days are given. Preliminary reports on this method of treatment are encouraging.

An attempt is being made to rehabilitate prostitutes and other promiscuous persons. At times, the Department must resort to court action in cases of flagrant violation of the moral code.

**Cancer and Other Chronic Diseases** This division is responsible for conducting a cancer-control program and is assisted in the endeavor by the Massachusetts Medical Society and the American Cancer Society (Massachusetts Division), Inc. The program has three objectives: the prevention of cancer, its early recognition and prompt adequate treatment, and studies — biologic, clinical and epidemiologic — to learn more about the disease. The major parts of the program include maintaining a cancer registry, conducting cancer statistical research, furnish-

ing information to both the profession and the laity and service to cancer patients.

Two cancer hospitals, eighteen cancer diagnostic clinics and one contemplated cancer clinic, together with free-tissue diagnosis service to all physicians in the Commonwealth, comprise the service elements of the program. Free service at the clinics is limited to the medically indigent, but experience has shown that relatively few patients are able to pay. Through these clinics and the two hospitals the Department is seeing approximately 10 per cent of all cases of cancer in the Commonwealth.

Education of the public is maintained through local co-operative cancer-control committees, whose chief function is to arrange meetings at which local physicians are invited to speak on cancer. Many thousands of these meetings have been held, and I should like to take this opportunity to thank the physicians of Massachusetts for so freely contributing to this effort.

#### SPECIFIC SERVICES OFFERED TO PHYSICIANS

##### *Postgraduate Education*

Through funds made available by the United States Public Health Service and the Children's Bureau, the Department can offer physicians postgraduate training in public health. Physicians who have graduated from an approved medical school and who have had one or more years of internship are accepted in the Department in a training position during which they receive a salary of \$300 a month for a period of field orientation. Subsequently, if they prove their worth and wish to continue in public health, they may elect to attend any of the ten schools of public health in the United States for an academic year, working toward the degree of master of public health. During their stay at the school, they are paid their tuition, traveling expenses to and from the school, and a stipend equivalent to approximately \$300 a month. Physicians who are interested in obtaining such training are expected to pursue careers in public health in the state, local or voluntary health agencies in Massachusetts. Some training is offered to other professional groups. Selected persons may be given a second year of training in public health or in one of the allied fields, provided they expect to work with the state health agency in this field.

With the co-operation of the Massachusetts Medical Society, the Department has been sponsoring postgraduate education of physicians in practice, especially of veterans who have returned after several years of service. Educational facilities have been made available through the postgraduate teaching facilities of the Massachusetts Medical Society, the Sanders Theater programs and, on occasion, special teaching clinics conducted by the Cancer Clinics and special courses devoted to such fields as care of the premature infant, well-child con-

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## CARCINOMA OF THE COLON AND RECTUM\*

JAMES W JAMESON, M D,† AND CLINTON R MULLINS, M D‡

CONCORD, NEW HAMPSHIRE

THE purpose of this presentation is to give our experience with all the cases of carcinoma of the colon and rectum that have come under our observation from September, 1936, to September, 1946. This experience seems to be of interest since few reports from such small communities as ours (with a population of about 28,000) are forthcoming.

We have tried to follow the most generally accepted methods of management as judged from past experience, observation of procedures in use elsewhere and a study of current literature for improvements in technic and care. We have also attempted to emphasize the importance of nutritional restoration, replacement of vitamin deficiencies, blood transfusions as indicated, fluid balance and careful supervision for complications, both preoperatively and postoperatively. The anesthesia has been almost entirely spinal, either in one dose or fractional, given either by the surgeon and watched by a nurse anesthetist or by a physician who was not a specialist in anesthesia. There have been no serious accidents or failures in this respect. Local anesthesia has been used for preliminary cecostomy when needed.

Sulfaguanidine, sulfasuxidine and sulfathalidine have been used since their introduction, and it is believed that they offer an added factor of safety at operation.

*Operative Technic*

Catgut sutures have been employed in most cases. Cotton sutures have recently been used, with satisfactory results. Retention sutures of heavy silk or nylon have been placed in most cases but were not used in the 2 cases in which the wounds disrupted, they seem to be a necessary precaution. All anastomoses of the intestine were of the open type, interrupted silk being used for the serosal sutures. It is believed that the added exactness of the open anastomosis more than compensates for the possible danger of contamination. In 24 cases in which this was done there were no deaths and no signs of peritonitis. Local sulfonamide therapy has been employed in all cases of anastomosis—usually 20 per cent microform sulfathiazole suspension in amounts up to 20 cc.

Early ambulation has not been carried out in these cases. There have been no cases, however, showing clinical signs of phlebitis or pulmonary embolism. No case with clinical signs of pneu-

monia or atelectasis has been observed. Wound infection has not been troublesome.

*Carcinoma of the Ascending Colon*

There were 14 cases in all, including 12 male and 2 female patients, and of these only 9 cases were considered resectable at operation, in 5 cases that were deemed inoperable because of involvement of other structures and fixation, 1 having a large abscess, palliative procedures were performed. The resections were all done in one stage, in spite of varying degrees of obstruction. There were no postoperative deaths. In the 6 cases in which operation was done three or more years ago, 4 patients, or 66 per cent, are living and well. Of the 2 patients who died, 1 lived seventeen months and succumbed with signs of recurrence and the other lived 10 months. The latter had a cecostomy performed before being seen by us, so that the prognosis seemed poor from the beginning. Of the operations done since 1943, 1 is a recent case, 1 patient is living and well nine months postoperatively, and another died after six months of metastases. The only postoperative complication was infection of the operative wound in 1 case. It seems that carcinoma of the ascending colon presents greater difficulty in diagnosis than any other area for both the roentgenologist and the physician.

The following report is that of a patient in this group who also had a separate lesion in the left transverse colon, which was not discovered until later.

J. R. (C.H. 52512) a 47 year-old woman was admitted to the hospital on January 26, 1943. She gave a history of rectal bleeding 9 months before admission. She was anemic and received liver and iron for several months before and after that episode. About 2½ months before entry she began to have abdominal cramps and loose stools. A barium enema given shortly before admission showed a lesion of the ascending colon.

The past history was irrelevant.

Physical examination disclosed a pale patient with a firm slightly tender movable mass about 9 cm in diameter in the region of the cecum.

Examination of the urine was negative. Examination of the blood revealed a red-cell count of 4,410,100 with a hemoglobin of 13.1 gm., and a white-cell count of 8600, with 58 per cent neutrophils, 27 per cent lymphocytes, 12 per cent monocytes and 3 per cent eosinophils.

At operation on February 2 the abdomen was explored through a right rectus-muscle-splitting incision. There was a typical growth in the cecum with no evidence of metastasis to the liver or local lymph nodes. The lesion was easily mobilized and removed, together with the terminal ileum and hepatic flexure of the colon and regional mesentery. An end-to-side ileotransverse anastomosis was carried out.

The pathological report showed a growth 6 cm in its greatest diameter just distal to the ileocecal valve, involving about half the circumference of the bowel. Microscopic

\*Presented at the annual meeting of the New England Surgical Society, Worcester, Massachusetts, October 4, 1946.

†Consulting surgeon, Concord Hospital.

‡Attending surgeon and joint chief of surgery, Concord Hospital.





Richard B. Cattell at the Lahey Clinic. One polyp showed malignant changes. Also of interest were 2 sisters, who had lesions of the descending colon.

# Carcinoma of the Rectum

There were 33 cases in this group, with 19 male and 14 female patients. Abdominoperineal resections were performed in 17 cases — one-stage in 16 and two-stage in 1, in these cases operations were done three or more years ago in 11, and 4 patients (36 per cent) are living and well. There were no postoperative deaths, but serious complications were troublesome. In 1 case the wound disrupted on the fifth day. This patient had liver metastasis at the time of operation. Another disruption occurred on the seventh day, with perforation of the small intestine and extensive soilage from the intestinal contents, repair of the perforation and suture of the abdominal wall were done in bed under local anesthesia, and the patient lived thirty-eight months without recurrence, dying of coronary thrombosis. This patient also had two distinct lesions, one of the rectum and one of the sigmoid.

One patient had a herniation of the small intestine through the pelvic floor, the obstruction being missed at the first operation. This patient was living and well forty-four months after operation. Another also had signs of obstruction postoperatively and was again operated on, but only extensive adhesions were found. The adhesions were considered as possibly due to the sulfathiazole suspension used at the first operation. This patient was well twenty-four months after operation.

There were 2 cases in which only local excision was done. In 1, in which a rectal polyp showed malignant changes, the patient was free of recurrence thirty-five months postoperatively. The other patient had extensive papillary changes, microscopically malignant, and local resection was performed after wide exposure by splitting of the sphincters anteriorly and posteriorly. This patient was free of recurrence and had no incontinence twenty-four months later. Radical operation was refused in this case.

Five cases were treated by radon seeds, 3 for palliative purposes, with little benefit, and 2 for possible cure. One of the latter patients refused surgery, and the general condition of the other seemed too poor for operation. Both had small lesions, which were found to be malignant at biopsy. One was living and well eight years, and the other five and a half years after operation.

Of 2 patients who were not treated, one died twenty-four hours after admission with perforation and peritonitis, and the other was almost moribund on admission.

## SUMMARY

Over a ten-year period 71 cases of carcinoma of the colon and rectum were seen. Of these, 49 were deemed to be operable, 4 of which were not treated radically for varying reasons. Forty-five were operated on for cure, with 1 postoperative death — a mortality of 2 per cent. Twenty-eight of this group were treated three or more years ago, and 13 are still living and well — a three-year survival rate of 46 per cent. Of 18 cases seen five or more years ago, 11 were treated for possible cure, and 7 were treated palliatively. Five of the patients treated survived for five years or longer.

The results leave much to be desired but are not wholly discouraging.

## DISCUSSION

DR. FRANK H. LAHEY (Boston). Three points ought to be stressed in connection with these cases, one of which has not been discussed. The principal one is that this is a favorable lesion, but even the satisfaction derived from the present good results ought not to mislead us regarding another fact that we have stressed again and again: the relation of polyps to cancer and the need for everyone to think of polyps as possibly precancerous.

Many patients have polyps. No one knows exactly what the incidence is, but it is probably at least 5 per cent. I urge again that every routine physical examination include a proctoscopic and sigmoidoscopic examination, which often discloses polyps that can be removed. It is obvious that not all of them are removed but, on the other hand, with each polyp that is removed the chances that the patient will have a cancer are reduced.

Proctoscopic examination of colostomies should be carried out after abdominoperineal resection because it is easy to proctoscope a colostomy before the patient goes home. There are definite occasions on which polyps are demonstrated that can be removed and the patient may well be saved from another carcinoma.

Surgeons are urged to review their personal experiences in operating on patients with carcinoma of the colon and rectum. I know that I have regarded as inoperable cases of carcinoma of the colon or rectum that would be considered operable today in terms of possible cure.

The difference between growth by extension and true metastasis is again stressed. I have in the hospital today a woman who is ready to leave; she had a carcinoma of the rectosigmoid that had perforated into the bladder. She has had a resection of the sigmoid, removal of the left tube and ovary, ligation of the left ureter and resection of two thirds of the bladder.

We used to think that these extensive procedures could not be done, but we have now done combined abdomino-sacral resections of the rectum, together with total hysterectomy and removal of the tubes and ovaries in 90 cases. Often the uterus is involved only by contact extension. Carcinoma of the sigmoid is frequently found on top of the bladder and can be removed by local removal of the portion of the bladder involved as in this series of cases recorded by Drs. Jameson and Mullins. They illustrate what can be done in relatively small communities if this group of cases can go into a limited number of hands.

We must face facts even if we do not like them, as I have learned over the years. In the beginning I was not adept at operations on the colon and rectum. It is only by experience that one acquires the ability to handle these late cases — that is, those with contact extensions to the jejunum, those in which the perineal fat is involved (in which all the perineal fat can be excised) and those that, by contact, have involved other loops of bowel.

I therefore re-emphasize the facts that these patients who have no other hope, provided they do not have distant metastases and the growth is only local, should all be given much better chances with more radical approaches than

we have often given them in the past, and that many of them will probably enter the group with five-year non-recurrence rates

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In all cases carcinoma of the large bowel was present or had been present.

The 2 patients in whom the lesions had previously been resected showed no evidence of recurrent disease

Sulfasuxidine was used in 3 cases, with an abnormal reaction to the drug in 1. Sulfathalidine was used in 5 cases, with no untoward reaction. The dosage for both drugs was the same — namely, 6 gm a day given in 1-gm doses at intervals of four hours. Usually, at 10 p.m. the dose was 2 gm, and the 2 a.m. dose was omitted. In the first 5 cases the drug was given for an average of three days before operation, but in the last 3, which have occurred during the past three months, sulfathalidine was given for ten days before surgery was done. The average total preoperative dose was 17 gm in the first 5 patients, and 62 gm in the last 3

In the patient who appeared to be sensitive to sulfasuxidine the drug was given into a defunctioned left colon. On the following day the temperature rose to 103°F, without a corresponding elevation of the pulse or any other signs or symptoms. Two days later the temperature was normal, and the resection was done without further complications. This patient was given 6 gm of sulfasuxidine a day, by mouth, for two days before closure of the colostomy. She seemed to have no drug fever at that time, but the temperature rose to 102°F each day for three days after the colostomy had been closed — there was no wound sepsis or other explanation for the fever. This case is the only one of this group in which the temperature rose above 100.6°F after large-bowel anastomosis by the open technic

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In each case the colon was widely opened and sutured by the open technic. Resection of the bowel was done in each case except the one with obstruction following a Mikulicz right colectomy

One resection of the sigmoid for scar obstruction was done without proximal vent except that provided by a Harris tube in the small bowel

Gas was passed by rectum in 7 of the 8 cases in an average of three and a half days after the resection, and a bowel movement by rectum occurred on the average in slightly less than seven and a half days

All wounds were treated by the method of delayed primary closure, the fascia being closed with interrupted No. 30 cotton suture, and the skin edges being closed by drawing up of the sutures or by clips on the second day. There was no wound sepsis

## CLINICAL NOTE

### TUBERCULOSIS IN THE AGED

#### REPORT OF A CASE

DAVID C DITMORE, M.D.\*

BOSTON

MILLER and Henderson<sup>1</sup> state that one of the greatest deficiencies in tuberculosis control has been the failure to make sufficient use of case-finding technics in the discovery of the elderly person with undiagnosed pulmonary tuberculosis. Meyers<sup>2</sup> believes that the presence of communicable pulmonary tuberculosis in persons over fifty years of age is higher than that in any other age period. The frequency of tuberculosis in the aged has been noted by others<sup>3-5</sup>

Laird<sup>6</sup> observes that the death rate from tuberculosis per 100,000 population in people over seventy years of age in 1940 was 91 for men and 68 for women and that, since there are 4,250,000 people over seventy years of age in the United States, the total number of deaths is not inconsiderable. Jennings<sup>7</sup> asserts that one of the persistent misconceptions held by the general public about tuberculosis

is that it never occurs in older age groups. He claims that even in medical circles the impression is current that old age affords protection against tuberculosis. Of 7212 patients admitted to Glen Lake Sanatorium, however, 13.8 per cent were over fifty years of age<sup>7</sup>, in 1 of these, a woman, the diagnosis was made for the first time at the age of sixty-four. Mariette<sup>8</sup> states that the oldest patient he remembers was a man ninety-four years of age at the time of admission to an institution

The following case illustrates the necessity of bearing constantly in mind the possibility of tuberculosis in the aged as well as in the young patient. Such cases, when unrecognized, represent a danger to the community

H. N. M., a 71-year-old man, was referred for examination on December 27, 1946. He stated that until 7 weeks previously he had always been perfectly well. Soreness at defecation had been present since that time, and it had been difficult to keep himself clean because of a discharge from the anus. He denied ever having a temperature, cough, sputum or weight loss

Examination of the anal canal disclosed the presence of two ulcers. One, located in the anterior commissure, was irregular in outline but measured approximately 1.5 cm in the widest diameter. The other, which was located on the left posterior lateral quadrant of the anal canal and measured approximately 3 cm in length and 2 cm in width, had the appearance of being the result of pressure from a pendulous external hemorrhoid extending across the canal from right to left, the point of contact producing a pressure necrosis

The edges of both ulcers consisted of a thin layer of skin without evidence of unusual thickening, induration or undermining. The base was covered with small tufts of rather indolent-appearing granulation tissue, which did not bleed easily on trauma. The surface was bathed with a copious grayish-yellow discharge that was easily removed with a

\*Instructor, Department of Proctology, Boston University School of Medicine; proctologist, Carney Hospital; consulting proctologist, Brookline Hospital

bottom-tipped applicator. Because of the unusual appearance of the ulcers they were excised and on examination showed changes typically present in tuberculosis. Ordinary treatment for 4 weeks produced no cure of the ulcers but complete healing occurred 2 weeks after the institution of streptomycin therapy.

On questioning the patient recalled that 2 years previously while having financial difficulties he had lost considerable weight, but he had attributed this to worry. He also admitted having a hacking cough in the morning and some sputum which he thought to be due to an old sinus infection.

A study of the sputum disclosed the presence of many colonies of *Mycobacterium tuberculosis*. X-ray examination of the chest showed a profuse mottling of all lobes of both lungs having much the appearance of miliary tuberculosis.

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## MEDICAL PROGRESS

### "FOLIC ACID" PTEROYLGLUTAMIC ACID AND RELATED SUBSTANCES (Concluded)\*

FREDERICK SARGENT, II, M.D.†

CHICAGO

#### THERAPEUTIC USES

The diseases in which pteroylglutamic acid has proved to be therapeutically effective are as follows: blood dyscrasias, including Addisonian pernicious anemia (hematologic phase), megaloblastic anemia of infancy, (?) refractory megaloblastic anemia, (?) tropical macrocytic anemia, nutritional neutropenia and nutritional macrocytic anemia, both primary (due to poor diet) and secondary (associated with pregnancy, pellagra, some cases of sprue syndrome, chronic alcoholism, gastric carcinoma and gastric resection), and gastrointestinal disturbances, such as certain cases of tropical and nontropical sprue, chronic diarrhea and celiac disease.

Conditions that have failed to respond to pteroylglutamic acid are certain blood dyscrasias (the neurologic phase of Addisonian pernicious anemia, idiopathic and secondary hypoplastic and aplastic anemia, hypochromic anemia of iron deficiency, anemia associated with cancer, leukemia and lymphoma, leukopenia following x-ray therapy, idiopathic agranulocytosis, agranulocytosis due to sulfonamides, thiouracil, arsenicals, aminopyrine and so forth and idiopathic and symptomatic thrombocytopenic purpura) and gastrointestinal disturbances, including idiopathic ulcerative colitis and certain cases of celiac disease, nontropical sprue and tropical sprue.

Only the more important of these diseases are considered below.

#### Addisonian Pernicious Anemia

Addisonian pernicious anemia is characterized by a disturbance of hematopoiesis and by combined-

system disease. Because these two phases respond differently to therapy with pteroylglutamic acid, each must be considered separately. Many cases of pernicious anemia in hematologic relapse have already been treated with this vitamin, with results that may be summarized as follows. In the peripheral blood, the reticulocytes begin to increase on the fourth to the sixth day, reaching a peak between the seventh and tenth days. The reticulocyte crisis is followed by a gradual rise in the red-cell count and the hemoglobin. In many cases the total white-cell count mounts, and the platelets increase in number. Simultaneously, the bone marrow undergoes a change from the characteristic maturation arrest to a normoblastic picture. A number of investigators have reported that, in spite of prolonged treatment or large doses of pteroylglutamic acid, the reticulocytic crisis is submaximal and the red-cell count and hemoglobin never reach normal values.<sup>11, 12</sup> If such patients are further treated with liver extract, the red-cell count and hemoglobin rapidly reach normal values. Meyer<sup>13</sup> reports that in a few cases small oral doses of pteroylglutamic acid (5 mg daily), in addition to 0.5 unit of liver extract, often give a reticulocytosis greater than anticipated and that with such therapy the remission is complete. In contrast, Davidson and Girdwood<sup>14</sup> have occasionally achieved excellent hematopoietic responses with as little as 1 mg of pteroylglutamic acid orally. Along with these hematologic improvements, the patient experiences a feeling of well-being, and the appetite returns to normal. Such symptoms as burning of the tongue, weakness, easy fatigability and dyspnea rapidly disappear.<sup>11, 12, 15</sup>

In contrast to the success in managing the hematologic phase, treatment of the neurologic manifesta-

\*Based on a talk presented at a meeting of the Bess Society of Boston University School of Medicine, Boston, on April 7, 1947.

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factor described by Castle. In addition, there is no anemia relieved by pteroylglutamic acid that does not also respond to therapy with liver extract.<sup>42</sup> These points comprise a list of disadvantages against the pteroylglutamic acid as the "new hope for anemic patients." Do any advantages accrue from the use of this vitamin? Two features have been suggested: oral therapy obviates repeated injections, but weighed against the possibility of neurologic relapse, this can scarcely be considered an advantage, and pteroylglutamic acid may be employed when patients are allergic to liver extract.<sup>43</sup> Against the latter consideration is the fact that patients allergic to pork-liver extract react satisfactorily to beef-liver extract given parenterally.<sup>44</sup>

#### *Blood Dyscrasias of Nutritional Origin*

The megaloblastic anemias of nutritional origin that respond to pteroylglutamic acid may be due either primarily to a poor diet or to secondary nutritive failure consequent to anorexia, poor absorption and utilization or increased requirements. The secondary cases are seen in such conditions as pellagra, pregnancy, the sprue syndrome, chronic alcoholism and gastric carcinoma. In cases of sprue, as pointed out below, the hematopoietic disturbance frequently fails to respond to therapy with pteroylglutamic acid. When neutropenia or thrombocytopenia occurs as a manifestation of nutritive failure, an increase in leukocytes and platelets will follow the administration of pteroylglutamic acid. If, however, the anemia is normoblastic or hypochromic (due to an iron deficiency) and the neutropenia and thrombocytopenia are idiopathic or secondary, administration of this nutrient effects no hematologic response.

#### *Refractory Megaloblastic Anemia*

Some cases of macrocytic anemia that present blood and bone-marrow pictures indistinguishable from pernicious anemia have no achlorhydria and fail to respond to parenteral purified liver extract. Such cases, however, respond to administration of crude extracts and yeast. These cases, which are called "refractory megaloblastic anemia," probably arise from poor dietary habits. Wills and her associates<sup>45</sup> have described such cases from India, suggesting that the name "tropical macrocytic anemia" be used to designate the condition. Wills<sup>46</sup> has produced a macrocytic anemia with a megaloblastic marrow in monkeys by the administration of a poor diet similar to that eaten by human patients with tropical macrocytic anemia. This monkey anemia is refractory to parenteral purified liver, but responds to a relatively purified substance from yeast preparations. Watson and Castle<sup>47</sup> suggest that this factor be called the Wills factor. The relations between the Wills factor and pteroylglutamic acid or between Wills monkey anemia and vitamin M deficiency have not been established,

but some workers have assumed that the two substances — pteroylglutamic acid and the Wills factor — are closely related, if not identical.<sup>48</sup>

One test of the relation between these substances is whether or not refractory megaloblastic anemia will respond to the administration of pteroylglutamic acid. Some cases called "refractory megaloblastic anemia" have been successfully treated with pteroylglutamic acid, but the criteria for so designating these particular cases is not clear. Two cases in this series seemed to fulfill the criteria for a diagnosis of refractory megaloblastic anemia. The patients showed a partial hematologic response to pteroylglutamic acid and were completely cured by further treatment with crude liver extract. One patient had a marked reticulocytosis on two occasions three weeks apart after treatment with purified liver extract, although there was no appreciable change in the red-cell count or the hemoglobin.<sup>49</sup> One wonders if this case might not also have responded to purified liver extract if more than two injections had been tried. The results of this study suggest, however, that the Wills factor and pteroylglutamic acid are not identical.

#### *Aplastic Anemia*

Although most authors<sup>51, 52</sup> report that aplastic anemia does not respond to pteroylglutamic acid, a few long-standing cases have shown variable but incomplete remissions following prolonged treatment with massive doses of pteroylglutamic acid.<sup>48</sup> The possibility that these patients were not merely undergoing spontaneous remissions was not satisfactorily ruled out.

#### *Sprue Syndrome*

The sprue syndrome consists of celiac disease in children and tropical and nontropical sprue in adults. There are a variety of reports in the literature concerning the response of this syndrome to pteroylglutamic acid.

Six cases of celiac disease have been treated with pteroylglutamic acid. In 3, a megaloblastic anemia accompanied the gastrointestinal disturbance. These cases have been reported only in summary, but they apparently responded with rapid clinical and hematologic improvement.<sup>53, 54</sup> Three other patients with hypochromic anemia were not benefited by pteroylglutamic acid.<sup>51</sup>

In the cases of nontropical and tropical sprue, there is likewise wide divergence of opinion regarding the usefulness of pteroylglutamic acid. So far as the associated anemia is concerned, some investigators<sup>55, 56, 57, 58, 59</sup> report striking improvement, whereas others<sup>60, 61, 62</sup> report no improvement. Part of the variation in response seems to be due to the degree of anemia at the beginning of treatment with pteroylglutamic acid. This vitamin fails to effect a complete remission of the anemia. If the anemia is severe, there will be striking improvement, but the

remission will be incomplete. If the anemia is only moderate (a red-cell count of about 4,000,000) there may be no response. These results suggest that in some cases of the sprue syndrome there is a deficiency of the Wills factor, as well as of pteroylglutamic acid. Many authors<sup>16, 23, 29, 38, 51-54</sup> report that the clinical improvement in cases of tropical and nontropical sprue is remarkable and dramatic. There is rapid restoration of appetite and sense of well-being. Epigastric distress disappears. More slowly, the body weight is restored to normal. Some cases fail to respond permanently, although they may show temporary improvement.<sup>55</sup>

Together with clinical improvement, there is marked improvement in gastrointestinal function. The bowel movements decrease in number and become normal in odor, color and consistence. The gastrointestinal mucosa is restored to its normal condition. Davidson and Girdwood<sup>51</sup> point out that in their series of 7 cases the most remarkable improvement of intestinal function occurred about the fifth day after the beginning of treatment with pteroylglutamic acid.

Metabolic improvement has also been noted by some workers. The blood levels of carotene and vitamins A and E are increased.<sup>7</sup> Some workers<sup>7, 38</sup> have reported restoration of glucose tolerance to normal. Others<sup>51</sup> have been unable to detect much change in fat absorption.

Further clinical study will be required before a final evaluation of the place of pteroylglutamic acid in the management of the sprue syndrome can be made. The hematologic results suggest that some other substances are necessary for a complete remission. The complicating roles of intestinal infestation with bacteria and parasites and of poor nutrition have not been adequately studied. A recent report by Suárez et al<sup>38</sup> emphasizes the fact that the response of this syndrome to pteroylglutamic acid may be facilitated by an accompanying adequate diet.

#### Other Gastrointestinal Disturbances

Carruthers<sup>19</sup> reports that 6 cases of chronic diarrhea of six weeks' to six months' duration of diverse etiology responded promptly to pteroylglutamic acid. All these patients had failed to respond to specific or symptomatic treatment. When 40 to 60 mg of pteroylglutamic acid had been given daily by mouth for two to five days, the diarrhea rapidly cleared, and there was general clinical improvement. The author suggests that a nutritional factor probably prolonged the abnormal stools.

Five cases of idiopathic ulcerative colitis have been treated unsuccessfully with pteroylglutamic acid.<sup>27</sup> Two of these patients apparently became worse during the course of therapy.

#### Cancer

From the experimental laboratory comes suggestive evidence that pteroylglutamic acid and related substances play a role in the growth of neoplastic tissue. Lewisohn and his associates<sup>56</sup> have shown that, in spontaneous breast cancer in mice, pteroyltriglutamic acid (fermentation *L. casei* factor) given intravenously daily in doses of 5 mg for four to six weeks caused complete regression of the neoplastic growth in about a third of the test animals. Pteroylglutamic acid (liver *L. casei* factor) in doses of 5 and 100 mg intravenously did not cause appreciable regression of neoplastic tissue. In fact, as compared with the controls, the incidence of lung metastases seemed greater. Perhaps other pteroylpolyglutamic acids that will prove efficacious in the treatment of human cancer will be synthesized.

#### SUMMARY

A review of the current literature reveals that the newest member of the vitamin B complex—popularly called "folic acid"—may prove effective in the management of a variety of blood disorders and certain abnormal gastrointestinal conditions.

This vitamin has been isolated and synthesized. Its chemical name is pteroylglutamic acid. Pteroylglutamic acid is identical with the *Lactobacillus casei* factor necessary for growth of *L. casei*, vitamin B<sub>9</sub> necessary for growth and hematopoiesis in the chick and vitamin M, which prevents cytopenia and a fatal sprue-like syndrome in monkeys. The related substances, pteric acid and pteroyltriglutamic acid (the active principle in fermentation *L. casei* factor), have been synthesized. The active material in the vitamin B<sub>9</sub> conjugate (or "folic acid" conjugate) has been identified as pteroylheptaglutamic acid, but this heptapeptide has not yet been synthesized. A compound containing thirteen molecules of glutamic acid has also been isolated from yeast.

An enzyme that hydrolyzes the tripeptides and heptapeptides to glutamic acid as well as pteroylglutamic acid has been discovered. This enzyme, known as vitamin B<sub>9</sub> conjugase, is abundant in such animal tissues as liver, kidney, pancreas and bone marrow.

Foods have been found to contain an unidentified substance—conjugase inhibitor—that impedes the hydrolytic activity of the enzyme vitamin B<sub>9</sub> conjugase.

Pteroylglutamic acid is widely distributed in nature but the amount present even in the best sources, such as spinach and liver, is only of the order of 100 microgm per 100 gm. The amount of pteroylglutamic acid in the ordinary diet is far less than that which is therapeutically effective. Until the nutritional requirements for this vitamin are known, however, a final evaluation of the richness of the nutrient in nature cannot be made.

Most of the naturally occurring vitamin is present as pteroylheptaglutamic acid

The important deficiency symptoms due to lack of this essential nutrient are failure of growth, cytologic disturbances and gastrointestinal disorders. The mode of action of pteroylglutamic acid is unknown, but it has been shown that although the heptapeptide is not efficiently utilized by patients with Addisonian pernicious anemia, pteroylglutamic acid can be utilized to some extent. The inability to make use of the heptapeptide is apparently due to failure to neutralize conjugase inhibitor

Pteroylglutamic acid is nontoxic for animals and is without toxic effect in large doses given orally or intramuscularly to man. Intravenous administration to human patients, however, is not recommended because of several cases of shock-like reaction that have followed when this route has been used

The currently recommended therapeutic dosage is 10 mg orally each day. For maintenance 5 to 10 mg daily has been found effective in most cases

Pteroylglutamic acid has proved effective in the treatment of a variety of blood dyscrasias, including Addisonian pernicious anemia, nutritional macrocytic anemia and neutropenia, macrocytic anemias of infancy and pregnancy and macrocytic anemias following gastric resection. The evidence for the response of refractory megaloblastic anemia to pteroylglutamic acid is still incomplete. An occasional case of aplastic anemia may respond to this vitamin

There is no anemia that responds to pteroylglutamic acid that does not also respond to liver extract

Pteroylglutamic acid does not cause a neurologic remission, nor does it prevent a neurologic relapse among patients with Addisonian pernicious anemia. Indeed, in some cases it seems to precipitate or cause a sudden outbreak of symptoms and signs due to predominant disturbance in the posterior columns. For these reasons, management of Addisonian pernicious anemia with pteroylglutamic acid is not recommended

Pteroylglutamic acid has no place in the management of hypochromic anemia due to iron deficiency, anemias associated with cancer, leukemia and lymphomas, and idiopathic and secondary (symptomatic) hypoplastic anemia, aplastic anemia, agranulocytosis and thrombocytopenic purpura

Evaluation of the effectiveness of pteroylglutamic acid in the treatment of the sprue syndrome is difficult, for different investigators have reported both successes and failures. More exact definition

of the clinical entities being studied is probably needed

Some cases of "chronic diarrhea" due to nutritive failure are benefited by pteroylglutamic acid

No benefit accrues from the use of this nutrient in idiopathic ulcerative colitis. In fact, some patients seem to be made worse by such treatment.

Because fundamental knowledge concerning the action of pteroylglutamic acid is still limited and because a full clinical trial has not been made, it is too early to venture an opinion on the final place of this nutrient in therapeutics

I am indebted to Drs. William B. Castle and Lionel Berk, of the Boston City Hospital for assistance in the preparation of this review

Presbyterian Hospital

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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BENJAMIN CASTLEMAN, M D, *Associate Editor*

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### CASE 33451

#### PRESENTATION OF CASE

A seventy-six-year-old woman was admitted to the hospital because of abdominal pain

For three years the patient had attacks of pain in the right lower quadrant of the abdomen, lasting only a few hours and associated with some constipation during these attacks. Eight days before admission, while riding in a car, she had a brief attack of pain, and finally, three days later, the pain became persistent. It radiated from the right lower quadrant to the back and to the left side of the abdomen but was not crampy in character. It was associated with nausea and vomiting of all solid food. There was no bowel movement in this interval, but she was able to pass gas.

The past illnesses and operations included an appendectomy thirty-five years before entry, a left salpingo-oophorectomy before entry, thyroidectomy twenty years before entry and a coronary thrombosis nine years before entry. She had had a Parkinsonian tumor for years. She had anginal attacks and had recently been taking digitalis.

Physical examination revealed a well nourished, dehydrated woman with a Parkinsonian tremor of the left arm and leg. The heart was enlarged, the border of cardiac dullness extending to the left. The whole abdomen was tender, especially in the right lower quadrant, where there was an exquisitely tender palpable mass measuring about 9 cm in diameter. This mass was also palpated in the right fornix on pelvic examination. Peristalsis was normal.

The temperature was 98°F, the pulse 95, and the respirations 22. The blood pressure was 250 systolic, 120 diastolic.

Examination of the blood disclosed a hemoglobin of 16 gm and a white-cell count of 11,400, with 86 per cent neutrophils. The nonprotein nitrogen was 47 mg, the fasting blood sugar 112 mg per cent, the total protein 6.5 gm per 100 cc, and the chloride 9 milliequiv per liter. A routine urine examination was negative.

A plain film of the abdomen showed gas-filled loops of small and large bowel. No gas was seen in the left colon distal to the hepatic flexure.

An operation was performed six hours after admission.

#### DIFFERENTIAL DIAGNOSIS

DR MARSHALL K BARTLETT. May we see the x-ray films?

DR STANLEY M WYMAN. The gas-filled colon described is seen extending from the region of the cecum to the splenic flexure. I cannot trace it with certainty below that point. There is some gas in the small bowel, but the bowel does not appear dilated. There are no areas of unusual calcification. I cannot outline the mass that is described.

DR BARTLETT. I was hoping for more help but must proceed with what is given. This patient was seventy-six years old and had a past history of two laparotomies and, in the past three years, attacks of pain in the right lower quadrant, usually lasting only a short time. The attack that brought her to the hospital lasted for five days, and the pain was described as always being in the right lower quadrant with radiation to the back and left side. It was not crampy, but had been associated with vomiting. What processes would cause that picture, together with the physical finding of an exquisitely tender mass palpable in the right lower quadrant and also felt by pelvic examination? Of course the first thing that comes to mind in a person with previous abdominal surgery is intestinal obstruction. Favoring that is the fact that she had not had a bowel movement for five days, although she had been able to pass gas during that period. To explain the mass we must assume that she had a loop of bowel that in some way became incarcerated or strangulated. It seems to me that at the end of five days with a situation of that kind there would have been more x-ray evidence of dilated small bowel than we have. I do not see how we can explain this picture of intestinal obstruction on the basis of something in the colon. Because of the situation in the right lower quadrant it would have to be something in the cecum presumably. Certainly, from the x-ray picture there was more gas in the right colon than elsewhere in the bowel. I therefore do not believe that this case will fit that picture.

What else could it have been? The appendix has been ruled out because it had been removed. There is the technical possibility of a residual section of appendix that developed into an abscess, but I cannot quite picture this as an abscess in the right lower quadrant. The normal temperature and moderate elevation of the white-cell count seem to me rather against something that had perforated and formed an abscess. Another fairly remote possibility is a Meckel's diverticulum. If it were diverticulitis of the sigmoid it would be more likely to be on the other side. A single diverticulum of the cecum is occasionally seen but is certainly rare, and again one would have to assume that it started with an acute inflammatory process with perforation and

abscess formation I think that the picture would have been a little different if this had been an abscess from any source

Regional enteritis must be thought of, but there is no particular feature of the history to point in that direction I suppose that in that condition a palpable mass can be formed, but I do not believe that it would have been of the type described in this case unless, again, it had perforated, with abscess formation

How about the pelvis as a source of this patient's problem? The left tube and ovary had been removed for a condition the nature of which we do not know To the best of our knowledge the right tube and ovary and the uterus were still present. Nothing is said in the history about the menstrual cycle We can assume, however, that the menopause had occurred many years previously It seems to me that an ovarian cyst is a definite possibility At her age that is more likely than a fibroid with a twisted pedicle I therefore believe the diagnosis of a twisted cyst best explains the sudden onset, the presence of an exquisitely tender mass at the end of five days, the normal temperature and the moderate elevation of the white-cell count

#### CLINICAL DIAGNOSIS

Twisted ovarian cyst.

#### DR BARTLETT'S DIAGNOSIS

Ovarian cyst, with twisted pedicle

#### ANATOMICAL DIAGNOSES

*Carcinoids of ileum, with metastasis to mesenteric lymph nodes*  
*Volvulus of ileum*

#### PATHOLOGICAL DISCUSSION

DR. FRANCIS INGERSOLL My preoperative diagnosis was a twisted ovarian cyst When the abdomen was opened a gangrenous loop of small bowel presented On the mesenteric border of the bowel there was a hard area, and deep in the mesentery of the bowel there was a similar hard mass Farther up in the ileum there was a small nodule in the bowel wall The bowel was infarcted because of a three-quarter turn at the level of the mass in the mesentery Inspection of the ovaries and exploration of the abdomen failed to show any evidence of cancer or evidence of anything that might be connected with the two nodules previously mentioned Three feet of gangrenous terminal ileum were resected, and a side-to-side anastomosis between ileum and cecum was performed

DR BENJAMIN CASTLEMAN The specimen we received was a loop of bowel, about 90 cm long, the middle third of which was thickened and gangrenous This gangrenous loop was twisted and adherent around an infiltrating mesenteric mass On opening the bowel we found in the region of the interad-

herence a submucosal tumor about 2.5 cm in diameter invading the wall of the bowel, but there was a definite space between the mesenteric mass and this nodule We noted a smaller but similar nodule about 25 cm away from the first nodule

Microscopical examination of these two tumors showed them to be argentaffinomas or carcinoids, and the mesenteric mass proved to be a metastasis from one of the tumors The carcinoid of the small bowel is a slowly growing tumor, and this one must have been present for years, finally metastasizing to one of the regional nodes It was the mesenteric metastasis that had produced the adherence and the volvulus Dr Ingersoll, will you describe the course following operation?

DR INGERSOLL The patient was an elderly woman, and we were pleased for the next ten days that the progress was satisfactory During that time she passed a little gas and had a moderate amount of drainage from the nasal tube, and we thought that she was over the worst part of the illness On the eighth and ninth days, however, she was nauseated and passed gas and watery movements by rectum On the eleventh day she was again nauseated Physical examination revealed active peristalsis, but there was a mass in the right upper quadrant. This mass seemed to be connected with the liver It was quite discrete and very easy to feel There was no spasm except over the mass, and the rest of the abdomen was soft and non-tender She was jaundiced It was apparent that she was a desperately ill woman, and that nothing further surgically could be done at that time. She was given supportive therapy and had a shaking chill in the afternoon and another in the evening At 4 in the afternoon she was quite deeply jaundiced, and the pulse, which had been 88 in the morning, was 130, and the temperature was 105°F The house officers were called late that night and said that she was more deeply jaundiced than she had been at 6 or 7 in the evening, when I had seen her She died early in the morning

DR CASTLEMAN Autopsy showed an acute condition of the gall bladder, which was distended, markedly injected and covered with fibrin A small stone, 1 cm above the ampulla of Vater in the common bile duct, was completely obstructing the lumen No other stones were found in the bile ducts or gall bladder The liver was enlarged and deep green

#### CASE 33452

#### PRESENTATION OF CASE

A seventy-two-year-old Negro entered the hospital because of swelling in the neck

Seven months before admission a swelling in the neck had been noted in the Out Patient Department of a neighboring hospital, and since that time the patient had observed that it did not change

appreciably in size. There had been no difficulty in breathing or swallowing and no toxic symptoms. He had lost 30 pounds in weight during the year prior to admission. Scoliosis of the spine had been present all his life and had become somewhat worse during the few years prior to admission. Twenty-one years before admission cough, weakness, weight loss and chest pain were noted, and a diagnosis of tuberculosis was made. Treatment consisted of rest at home, and apparent recovery ensued. There had been no hemoptysis and no recent cough. During the two months before admission he had been bothered by dyspnea and left precordial pain on exertion. There was no ankle swelling.

The patient admitted to having had gonorrhea in his youth and during the three years before admission suffered from urinary hesitancy and a weak stream. A year after the onset of these complaints a sinus appeared in the perineum, which drained pus but never urine or fecal material. This never actually bothered him until three months before admission, when he noted the onset of frequency of urination associated with considerable perineal pain. There was also pain on moving the bowels. For two weeks before admission he had been bothered by marked anorexia and occasional attacks of "dry heaves." He admitted to having always liked cabbage and to having eaten much of it all his life.

Physical examination showed a well developed but emaciated man. The thyroid gland was diffusely enlarged to about four times the normal size, moderately firm and nontender. No bruit was heard. The spine showed moderate scoliosis, with convexity to the right in the dorsal region and to the left in the lumbar region. There were dullness, decreased breath sounds and tubular breathing over the left apex and a high diaphragm without movement on the left side. Over the right apex the breath sounds had a tubular quality, and whispered voice was increased. The heart was enlarged to percussion, the sounds were of fair quality, and there were occasional premature beats with compensatory pause and no pulse deficit but notable variation in force of beat. No murmurs were heard. There was moderate costovertebral-angle tenderness. The right testicle was atrophic, and the cord was thickened. There was a sinus at the perineoscrotal angle. Rectal examination was unsatisfactory because of extreme generalized tenderness.

The temperature was 99°F, the pulse 80, and the respirations 20. The blood pressure was 120 systolic, 70 diastolic.

The urine showed a +++ test for albumin and contained innumerable white cells. The hemoglobin was 98 gm per 100 cc, and the white-cell count 19,500, with 81 per cent neutrophils. The non-protein nitrogen was 70 mg per 100 cc. A smear from the perineal sinus was negative for acid-fast bacilli. Urine cultures revealed abundant colon

bacilli and nonhemolytic streptococci. Smears showed no tubercle bacilli.

An x-ray film of the chest disclosed marked kyphoscoliosis. The left leaf of the diaphragm and the left border of the heart could not be traced, and only a few cystic areas of lung could be seen on the left side. The right lung showed mottled areas of increased density scattered throughout all lung fields, particularly at the apex. The hospital course was febrile, with temperatures as high as 102.5°F and with white-cell counts as high as 38,000. Catheterization revealed 3000 cc of residual urine, the urethra was dilated, and a Foley catheter inserted. Digital examination on the third hospital day ruptured a perirectal abscess into the rectum. On the fifth hospital day the patient was found to be cold, clammy and unresponsive. The pulse was 130, the respirations 40 and grunting, and the blood pressure 80 systolic, 20 diastolic. He died later on the same day.

#### DIFFERENTIAL DIAGNOSIS

DR EARLE M. CHAPMAN: May we see the x-ray films?

DR STANLEY M. WYMAN: It is impossible to outline the left leaf of the diaphragm. I cannot describe the heart, which is inadequately defined. The left side of the chest contains numerous, rather thick-walled, cyst-like areas, with no obvious fluid in the rounded areas. The possibility of a herniation of colon into the chest might be mentioned in passing. I do not consider that very likely, however. This is the scoliotic spine, with kyphosis also apparent in the lateral view. Throughout the right lung there is mottled density, which is rather concentrated at the apex. The density is somewhat linear but also rather soft and mottled in the lower two thirds of the lung field. I believe that this is old chronic disease in the left side of the chest. What is going on in the right side is hard to say.

DR CHAPMAN: Does it look like active tuberculosis to you?

DR WYMAN: It might be a bronchial spread or, less likely, a miliary spread of tuberculosis, although it does not look typical of the latter. I do not see cavity formation, but cavities might be concealed in the right apex.

DR CHAPMAN: The physical findings were suggestive of cavitation.

DR WYMAN: In this view the rarefaction can be seen. It could be cavitation.

DR CHAPMAN: Do you think that that is cystic disease of the lung on the left?

DR WYMAN: Yes, it might be due to a sclerosing process, possibly tuberculous, with bronchial involvement.

DR CHAPMAN: The mechanical factor compressing the left lung must be considered. We know that patients with severe scoliosis sometimes de-

velop emphysematous blebs as an attempt at compensation

DR WYMAN I think that this is more than emphysema. These are thick-walled, cyst-like areas in the lung, not thin-walled emphysematous blebs. Perhaps in keeping with that is the suggestion of thickening of the pleura along the lateral chest wall.

DR CHAPMAN It is not surprising that there was severe dyspnea. Evidently, the vital capacity was not determined, but I assume that it was markedly reduced. This man had known tuberculosis, and toward the end he must have had bilateral extensive tuberculosis with cavitation and with perhaps more recent spread on the right. An interesting clinical point in patients with this degree of tuberculosis is that they have dyspnea out of proportion to the signs on examination. The history is compatible with that diagnosis, but there was something else going on—that is, a perirectal abscess, which was drained. In addition, the urine contained a great deal of albumin, and there were signs of uremia. The question arises, Was this on an obstructive basis from the perirectal abscess, or, in the face of this long-standing disease, did the patient have amyloid disease of the kidney? Little or nothing about renal function is indicated. It is stated that there was tenderness in the costo-vertebral angle and retention of urine, with 300 cc of residual urine, and that the patient was in uremia. I do not see how it is possible to establish which of these two possibilities was present, but we must consider the possibility of amyloid disease of the kidney.

Then we come to the matter of thyroid disease, because of this mass in the neck, and I assume that that is why I was asked to discuss this case. The patient first came to the hospital because of swelling of the neck, and a goiter could be felt that was about four times the size of a normal thyroid gland and was moderately firm and nontender.

I wondered about thyroid hyperplasia, but there is no evidence in this record of symptoms or signs of hyperthyroidism, so that we can exclude that diagnosis. With all this tuberculosis in the body,—at least I assume it to have been that,—was this tuberculosis of the thyroid gland? That is extremely rare. It does happen, but tuberculosis in a gland as vascular as the thyroid is rare indeed. I doubt if we have ever seen a case in this hospital, although it has been reported. I have never seen a case, and I recall a recent case at the Baker Memorial with a hard nodular mass and the signs of tuberculosis in which Dr Donaldson operated, thinking that it was tuberculosis of the thyroid gland. They were tuberculous nodes densely adherent to the gland but not invading it. Is that correct, Dr Donaldson?

DR GORDON A DONALDSON That is my recollection.

DR CHAPMAN Another important point is that the mass was nontender. Tuberculous thyroiditis would produce signs of inflammation that would have been evident on physical examination.

Could this have been amyloid disease of the kidney and the thyroid gland? One must consider amyloid in the thyroid gland. I had not been aware of that diagnosis until a case was discussed at Grand Rounds a few months ago of a man with rheumatoid arthritis, who had such a mass, which histologically proved to be amyloid. One must therefore keep that possibility in mind, but another case in the same year would be a great rarity. Simply on the law of chances, I should say that it was not amyloid.

Since this man liked cabbage, which is one of the common goitrogens because of its content of cyanate ion, we come to the most likely possibility—that is, an iodine-deficiency goiter. Astwood<sup>1</sup> and the VanderLaans<sup>2</sup> have recently explained the mechanism by which this occurs. Another possibility is a type of thyroiditis known as Hashimoto struma. In some cases of the Hashimoto type giant-cell formation simulating tuberculosis has been described. If Dr Mallory says that there were giant cells I can still say that does not prove the disease to have been tuberculosis. So much for the differential diagnostic points concerning the thyroid gland.

Then we come to the final episode. Why did this man die so abruptly? I am sure that I do not know. There are two or three things that come to mind. He was doing fairly well until he suffered the shock of rupture of the perirectal abscess. If he did not die from the shock of that, he might have had sepsis from it. He had kyphosis, the heart was enlarged, and he had premature beats, and irritability of the heart, suggesting that the myocardium was not a very healthy one. As a terminal episode he may have had severe heart failure or cardiac infarction. I see no way of making the diagnosis.

In conclusion, I shall say that he had tuberculosis, bilateral and extensive, with cavitation, perirectal abscess, questionable prostatic tuberculosis and questionable amyloid kidney with uremia, and that in my judgment this was an iodine-deficient goiter induced by goitrogens and not hyperplasia, or amyloid disease, tuberculosis or Hashimoto struma.

DR CHARLES E RICHARDS I wonder why Dr Chapman has not mentioned carcinoma in the differential diagnosis.

DR CHAPMAN There is no mention of the gland's being fixed. It seemed unlikely that it would be carcinoma, but I suppose that I could have included that diagnosis to be encyclopedic.

DR DONALD S KING I think that he had active tuberculosis, but I wonder if one could prove it. I should have to guess that he had it, but I am not absolutely certain.

DR TRACY B MALLORY I almost hesitate to admit that this patient was in the hospital for five days and that no sputum examination was ever made

PROFESSOR HERMAN SIKL Perhaps blockage of the bronchus produced fibrosis of the lungs

DR HELEN S PITTMAN When I first saw this man he was in the Out Patient Department, and I had no idea what was the matter basically. Obviously, he had an enormous thyroid gland—not hard or tender and not fixed, but causing some pressure. I thought that he had Pott's disease and a tuberculous draining abscess, secondary to that, and was quite sure that he had old pulmonary tuberculosis and arteriosclerotic heart disease

DR CHAPMAN That is helpful, and it makes me think more of carcinoma, as Dr Richards brought out. I thought that this was a stationary lesion. As you describe it, it makes one think of carcinoma simplex, a rapidly spreading type. The man was not very observant, and the thyroid gland seems to have been growing much faster than one would gather from the history

DR PITTMAN The patient was not a careful observer, but our impression was that the gland was growing rapidly

#### CLINICAL DIAGNOSES

Adenoma, nontoxic, of thyroid gland  
Tuberculosis of vertebrae  
Perirectal abscess and prostatitis

#### DR CHAPMAN'S DIAGNOSES

Tuberculosis, bilateral, extensive, with cavitation.  
Perirectal abscess  
Prostatic tuberculosis?  
Amyloid kidney(?), with uremia  
Iodine-deficient goiter (cyanate)

#### ANATOMICAL DIAGNOSES

*Pulmonary tuberculosis, chronic*  
Bronchiectasis  
Cor pulmonale, slight  
Tuberculosis of prostate gland, seminal vesicles and epididymis, active  
*Amyloid goiter*  
Amyloid nephrosis, slight

#### PATHOLOGICAL DISCUSSION

DR MALLORY The heart did not show any coronary disease. It was slightly hypertrophied, particularly the right ventricle, justifying the diagnosis of cor pulmonale. This is not uncommon in kyphoscoliosis, but there was also severe pulmonary disease. The pulmonary picture was very complicated. There was extensive old tuberculosis, but it was mostly fibrous, with encapsulated caseous foci, and relatively inactive. The cavities that Dr. Wyman demonstrated were greatly dilated bronchi, which, at the time of autopsy, were filled with purulent secretions. I believe that bronchiectasis was perhaps the most important factor in the patient's death. The vertebral column was, of course, greatly twisted, as the x-ray films show, but there were no collapsed vertebrae that would permit a diagnosis of Pott's disease. The most active tuberculosis found was in the lower urinary tract. The prostate, seminal vesicles and right epididymis all showed involvement.

Our interest naturally centers around the thyroid gland, which showed parenchymal atrophy, great numbers of fat cells and masses of homogeneous material that had the staining reactions of amyloid. This makes the second amyloid goiter in a short time. Amyloid is a rare disease in this area. These are the only 2 cases of amyloid goiter that I have seen. Perhaps Professor Sikl is more familiar with them in his material in Prague.

PROFESSOR SIKL No

DR LOUIS K DAHL Was there any amyloid anywhere else in the body?

DR MALLORY Traces were present in the kidneys but not in the spleen, the liver or the adrenal glands—the other usual foci.

DR ALLAN G BRAILEY Is it apparent why the patient died?

DR MALLORY We have no explanation why he died or when he died. Patients with scoliosis are very prone to sudden cardiac death without any warning or premonitory signs. He had, in addition, active tuberculosis and severe bronchiectasis. Perhaps, as Dr. Chapman suggests, the rupture of the perirectal abscess was enough to tip the balance.

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## A WARNING REGARDING THE USE OF FOLIC ACID

An alarming incidence has been reported of neurologic relapse or progression of pre-existing neurologic lesions in cases of pernicious anemia treated with folic acid, the term being used to indicate synthetic pteroylglutamic acid. Sargent's review, presented elsewhere in this issue of the *Journal*, places the incidence of such neurologic lesions at about 20 per cent during a period of one year or less of therapy. More recent studies show an even higher rate. Ross<sup>1</sup> observed an incidence of over 50 per cent in 21 cases. In Wagley's<sup>2</sup> series of 10 cases, 8 developed neurologic lesions or progression of pre-existing lesions within eight days to twelve months after the institution of folic acid therapy. Two cases of sprue have been noted in which neurologic

lesions occurred during folic acid therapy.<sup>3</sup> In one of these cases, the lesions recurred during a second course of folic acid therapy. These figures are obviously in striking contrast to the well known results with therapy by liver extract or gastric preparations, which in adequate dosage almost invariably arrest existing neurologic lesions or prevent the subsequent development of nerve changes. Indeed, these findings suggest that substitution of the newer remedy places the patient's continued health in jeopardy.

In most of the cases treated with folic acid the patients were subjectively in good health, and the red-cell count and hemoglobin had returned to normal levels at the time that the neurologic signs appeared. Increasing the dosage of folic acid nevertheless failed to prevent progress of the neurologic lesions. These have occurred in cases receiving as much as 500 mg daily, or about twenty-five times the average amount required for the relief of the hematologic abnormalities. It appears, therefore, that the neurologic changes cannot be ascribed to inadequate folic acid dosage.

Three possible relations of folic acid to the neurologic disturbances exist. First, folic acid may merely be allowing the disease to run its natural course so far as the nervous system is concerned. This may actually have happened in some of the reported cases. In contrast to the neurologic signs in combined system disease, however, few cases have shown unequivocal evidence of lateral column involvement, despite severe and extensive posterior column disturbance. Secondly, Heinle and Welch<sup>4</sup> have suggested that folic acid in relieving one deficiency accentuates another, which is in turn responsible for the neurologic changes, as occurs occasionally with other members of the vitamin B complex. Thus, cure of pellagra by nicotinic acid may result in manifest thiamine deficiency. The third explanation is that folic acid may actually exert a positively deleterious influence on the nervous system. Thus, by some close chemical relation to substances required to maintain the integrity of the nervous system, folic acid may competitively interfere with the nutrition of the spinal cord just as certain vitamin deficiencies in experimental animals may be caused by closely related chemicals.

Thiamine deficiency, for example, may be induced by the administration of pyriethamine, and pantothenic acid deficiency by pantoyletaurine. Ross<sup>3</sup> has recently suggested that pteroylglutamic acid may interfere with the metabolism of glutamic acid by the central nervous system, which, according to a preliminary observation by Pearson,<sup>5</sup> it appears to do, at least in vitro.

A positively injurious effect of folic acid therapy is consistent with the following features of the neurologic disturbance. In many cases an explosive onset and spread of the neurologic lesion has been noted. On the other hand, whereas combined system disease may start acutely, it does so only rarely. Several cases have been reported in which liver extract had been taken sporadically and in amounts inadequate to maintain normal blood levels for periods as long as ten years, without the development of nerve lesions. Yet on changing to folic acid therapy the sudden onset of severe neurologic manifestations occurred within a few weeks.<sup>6</sup> Ross<sup>1</sup> observed 1 case in which the addition of liver-extract therapy produced little if any improvement in the neurologic picture until folic acid administration was stopped. Indeed, the usual improvement in neurologic function occurring on withdrawal of folic acid and the institution of liver-extract therapy may be ascribed as much to the removal of the causative factor as to a response to the liver extract. Thus, giving liver extract with folic acid may not guarantee that neurologic disturbances will not develop. A further suggestion of a toxic action of folic acid is that the incidence of neurologic changes during folic acid therapy appears to parallel to some extent the dosage and frequency of administration. In cases treated with large daily doses of 25 to 50 mg the incidence has been highest, whereas in a series receiving only 75 mg once a week, the incidence was but 1 out of 11 cases. A possible explanation is that a large portion of a single dose is lost in the urine within twenty-four hours and that consequently with weekly administration the nervous system is exposed to very little folic acid in the intervening six days.

The inadequacy of folic acid in the treatment of pernicious anemia is also noted in the incidence of glossitis with such therapy. In Hall's<sup>7</sup> series 7 pa-

tients showed glossitis before commencement of therapy. Three improved temporarily and then relapsed, and 1 became worse. In Wagley's<sup>2</sup> series, 2 patients developed glossitis for the first time while on folic acid therapy, and another showed marked increase in the soreness of the tongue and developed glossal petechiae. Such developments are virtually unknown with adequate therapy by liver or stomach preparations.

Pteroylglutamic acid is the first hematopoietic substance in pernicious anemia to be chemically identified. When it became available in pure synthetic form about two years ago, it appeared likely to replace the older empirical but highly effective preparations of liver or stomach. Now, however, sufficient evidence has accumulated to justify a warning that synthetic pteroylglutamic acid (folic acid) should not be used in the treatment of pernicious anemia. In view of the reports of folic-acid-induced neurologic lesions in sprue,<sup>3</sup> this restriction should probably apply also to other nutritional macrocytic anemias. Folic acid has failed to be effective in other conditions in which liver or stomach preparations have also failed to benefit the patient. Consequently the use of folic acid as a therapeutic agent appears to offer no new benefit but only risk to the patient.

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EPIDEMIC LEAD POISONING

It is close to a century since the medical profession began to warn the public of the danger of lead poisoning. They did it poetically in those days, too, Dr. Samuel L. Dana, of Newton, told the city officials of Lowell, "It is found by experience that the young, the delicate, soonest succumb under the effects of lead drank in their daily drink, and like

the dew of heaven, descending on all, the gentlest and fairest feel the chill which soon closes in death."

In recent years the public has been amply warned of the lead hazards by which it may be surrounded. Emphasis has sometimes been mistakenly placed by the medical profession, as when it warned against lead painted toys and children's cribs only to find that none of the toy or crib manufacturers used lead in their paints. The vast expansion in the use of lead by modern civilization, however, makes a far wider field for exposure than that produced by painted surfaces, even including those painted with the brand that is reputed to "cover the world."

Approximately a million tons of lead are used each year in the United States. Symptoms from the absorption of this metal are now almost wholly confined to those who are exposed in industry. The largest single user of lead is the storage-battery industry, and although poisoning may and does occur in this and other industries, it is, on the whole, well controlled. In nonindustrial life it is only under peculiar and unusual circumstances that lead poisoning appears, but several epidemics, which extend back to 1933, have been recorded that seem to be difficult to approach from the point of view of public education. These epidemics were due to the use of discarded storage-battery casings for fuel. The casings burn readily but are encrusted with lead salts, which become volatilized in the smoke and fumes. When such fumes escape through a leaky stove they can readily poison a whole family. The most recent account of this sort of epidemic appeared in an article by Cooper<sup>3</sup> in which an outbreak in Staunton, Virginia, is described. Health authorities discovered that war-time scarcity of fuel had led a whole neighborhood into the habit of burning discarded battery casings, with the result that 17 children were found to have latent or toxic lead poisoning. It is interesting to note that Dr. Cooper agrees with Dr. Dana, quoted above, for he writes concerning one aspect of the subject, "In epidemics of lead poisoning in which both children and adults have been exposed in the same manner and amount, children are uniformly found to be more susceptible, particularly those under four years of age."

With the coming of colder weather, and with the continuation of a fuel supply that is neither abundant

nor cheap, a word of warning regarding this possible source of lead poisoning may be appropriately placed in the minds of physicians, public-health officials and even legislators, for there could be a law to regulate the disposal of discarded battery casings—many less rational laws have been enacted.

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### MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of data can be avoided.

#### APPOINTMENT OF DR. H. QUIMBY GALLUPE

Dr. H. Quimby Gallupe of Waltham, has been appointed by the president of the Massachusetts Medical Society secretary *pro tempore* to complete the unexpired term of Dr. Joseph Garland, who resigned to assume the editorship of the *New England Journal of Medicine*. Dr. Gallupe's appointment dates from November 1, 1947, when his predecessor's resignation became effective.

Dr. Gallupe is well known to the members of the Society for the exceptional efficiency with which he has performed his duties as secretary of the Massachusetts Board of Registration in Medicine over a period of nearly six years, and for his authorship of the Gallupe Plan, first put into operation at the Waltham Hospital two years ago.

The new secretary graduated from Tufts College in 1911 and from Harvard Medical School in 1918. He is surgeon-in-chief of the Waltham Hospital. In addition to his position as secretary of the Board of Registration in Medicine he is secretary of the Board of Registration in Nursing, chairman of the Approving Authority for Medical Schools and secretary of the Approving Authority for Nursing Schools. In the Massachusetts Medical Society he has served long as counselor from the Middlesex South District and, in addition, has been chairman of the Committee on Arrangements, chairman of the Committee on Membership and Finance and supervising censor.

His broad experience should be a distinct asset to the Society.



## A HUNDRED YEARS AGO

Dr Henry J Bigelow reports the unusual case of Jane McMurphy of Derry, New Hampshire. She is 17, small in stature, and of healthy appearance. Five years ago a piece of tobacco was inserted in her right ear by an old woman for earache. Of the piece of tobacco the patient saw no more at the time, but at the end of a month and for the subsequent months a physician succeeded in removing a portion of what was said to be tobacco, and at the end of a year two more fragments were extracted. In March 1846, the patient while lying in bed first heard a noise. It commenced suddenly and since then it has continued with little intermission. A person sitting in the room with this patient, hears a distant muffled sound, which might easily be mistaken for the rapid dropping of water into the bowl of a closed washstand. The sound may be conveyed by the words *click click*, or occasionally *click-click*, *click-click*, etc. The patient being requested to open her mouth, the sound becomes surprisingly distinct and audible, all the beats being apparently stimulated by the effort or by the contact of the air and the ticking becomes rapid. There is no discoverable discharge of pus or blood. The sound may be in an alternate opening and closure of the moist mouth of a sac, by which a bubble of air is expelled at each contraction, and a bubble sucked in at each dilation of its cavity. Such a sac exists between the vocal cords, or might be formed at one extremity of the os hyoides, with a fistulous opening. Such a solution of the cause of this singular sound is far from satisfactory, yet it is difficult to adduce any additional evidence of its nature. During her residence in the Hospital, Dr B deemed it unnecessary to harass the patient by repeating applications which seemed to have been faithfully tried, and the patient was altogether unwilling to submit to the division of one of the pillars of the palate which he proposed to her. — From a recent conversation with a medical practitioner belonging to the State of Tennessee, we learned the novel fact that a decided advantage is realized by consumptive patients in the middle and southern states in going North instead of South. Here the opinion is universal that persons with irritable lungs and more especially such as have a decided tendency to phthisis should go somewhere South. Without contending with anyone on the doctrines of contraries, as going South from the North, and North from the South, to allay symptoms and tendencies similar in character, we prefer that those most familiar with the results of such practice should discuss the subject — and whatever light may be exhibited, if it is truly light, will be received by us and the pro-

fession with feelings of gratitude. — At Meredith Bridge, N H, Mr B F Palmer carries on the manufacture of artificial limbs to a degree of perfection that both astonishes and delights all who have examined his ingenious life-like looking workmanship. Should the Mexican war continue much longer, the demand upon Mr Palmer's establishment must actively increase. — Dr Channing, having been Dean of the Medical Faculty of Harvard College for twenty-two years, has resigned the office, and Dr Holmes has been appointed in his place. — H K, a farmer, aged about 45, stout and healthy, of sanguine temperament, much addicted to inebriety, and very quarrelsome while under the influence of liquor, on August 19th, 1840, while intoxicated, undertook to chastise a small man. The latter, not feeling a disposition to submit to a drubbing, shot Mr K with a shot-gun loaded with shot and tow wadding, the muzzle of the gun being in contact with the left side of the epigastric region. Mr K fell, as if dead, and was conveyed home by four men in a sheet. On medical examination there was a large opening in the left side, as broad as a man's hand and about as long, indeed it looked as if his whole side had been torn away. He was immediately given a little of his favorite beverage, to wit, brandy and water, and bottles of hot water were applied to the axillae and between the thighs. On further examination it was found that the seventh and eighth ribs had been torn off from the attachment at the sternum to within three inches of the spine, together with all their appurtenances, the pleura included — thus exposing the lungs, diaphragm, stomach and pericardium<sup>1</sup>. Most of the wadding was removed, and some of the fragments of the missing ribs. In the course of time Mr K recovered his former health and strength, he also returned to his former habit of dissipation and has had many a pugilistic contest since. In consequence of the loss of two ribs, he leans considerably to the left side. The case presents several points of interest. Here was a man with almost half of his left side torn off, thus admitting a free current of air not only into the pleura, but lungs and whole cavity of the chest. He survived contrary to the teaching that it is death for air to penetrate through the thoracic parietes, and contrary to the aphorism of Hunter, "that those who always live above par are extremely liable to sink when attacked by disease or injury." He felt no inconvenience nor unpleasant consequences despite the presence of a silver tube which he was forced to wear for several months to drain the pleural cavity. — Extracted from the *Boston Medical and Surgical Journal*, November 1847

R F

# MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR AUGUST 1947

### RÉSUMÉ

DISEASES	AUGUST 1947	AUGUST 1946	SEVEN YEAR MEDIAN
Chancroid	2	0	1*
Chicken pox	179	123	123
Diphtheria	17	20	11
Dog bite	1033	1019	1025
Dysentery bacillary	9	1	15
German measles	41	46	46
Gonorrhea	303	365	374
Granuloma inguinale	1	0	0*
Lymphogranuloma venereum	1	0	0*
Malaria	7	21	13
Measles	125	400	296
Meningitis, meningococcal	0	4	5
Meningitis, Pfeiffer bacillus	1	2	1
Meningitis, pneumococcal	0	0	1†
Meningitis, staphylococcal	0	0	0†
Meningitis, streptococcal	0	0	0†
Meningitis, other forms	1	0	0†
Meningitis, undetermined	3	4	4†
Mumps	170	142	271
Pneumonia, lobar	17	29	76
Poliomyelitis	80	62	45
Salmonellosis	19	45	24
Scarlet fever	72	110	195
Syphilis	187	310	341
Tuberculosis, pulmonary	181	233	252
Tuberculosis, other forms	12	18	19
Typhoid fever	2	5	5
Undulant fever	7	6	5
Whooping cough	475	498	508

\*Three-year median.  
†Five-year median.

### COMMENT

Diseases above the seven-year median are chicken pox, diphtheria, dog bite, lobar pneumonia, poliomyelitis and undulant fever.

Diseases below the seven year median are bacillary dysentery, German measles, gonorrhea, malaria, meningitis, meningococcal meningitis, mumps, salmonellosis, scarlet fever, syphilis, pulmonary tuberculosis, tuberculosis (other forms), typhoid fever and whooping cough.

Diphtheria incidence is continuing the seasonal decline—17 cases compared to 20 in July. The trend will undoubtedly reverse early in the fall.

Poliomyelitis has increased from 21 cases in July to 80 this month. The seven year median incidence is 45. The disease will probably show an early seasonal peak in contrast to the late peak in 1946.

This is the first month in which no cases of meningococcal meningitis were reported since 1940.

### GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston 9, Canton 1, Chelsea, 1, Medford, 2, Melrose 1; Revere, 2, Saugus, 1, total, 17.

Dysentery, amebic, was reported from Boston, 1, total 1. Dysentery, bacillary, was reported from Beverly 1, Boston, 2, Cambridge, 1, Gloucester 1, Lawrence 1, Worcester, 3, total, 9.

Lymphocytic choriomeningitis was reported from Pittsfield, 1, total, 1.

Malaria was reported from Boston 3, Lynn, 2, Manchester, 1, Newton 1, total, 7.

Meningitis Pfeiffer bacillus was reported from Worcester 1; total 1.

Meningitis, streptococcal, was reported from Norwood, 1, total, 1.

Meningitis, other forms, was reported from Brookline, 1; total, 1.

Meningitis, undetermined was reported from: Dracut, 1, Haverhill, 1, Springfield, 1, total 3.

Poliomyelitis was reported from Andover, 1, Arlington, 2, Attleboro 1, Beverly, 2, Boston 9, Brockton 1; Cambridge, 6; Carleton 2, Dighton 1, Fairhaven 2, Falmouth 1, Fall River, 5, Franklin, 1, Freetown, 1, Great Barrington, 1, Hull, 1; Ipswich, 1, Lenox, 1, Lowell, 1, Lynn, 1, Middleboro, 1, Milford, 1, Milton, 1, New Bedford, 3, New Marlboro, 1, Newton, 4, North Attleboro 2, Northampton 1;

Northfield, 1, Pittsfield, 2, Revere, 1, Salem, 3, Somerville, 2; Southbridge, 1, Stoneham, 1, Taunton, 4, Waltham, 1, West Stockbridge, 1, Weston, 1, Westwood, 2, Winthrop 2, Worcester, 3, total, 80.

Salmonellosis was reported from Beverly, 2, Boston 2, Cambridge, 1, Chatham, 1, Lowell, 1, Monterey 2, Nauck, 1, New Bedford, 1, Newton 1, Salem 1, Taunton, 1, Waltham 1, Watertown 2, Winchester, 1, Worcester, 1, total, 19.

Trachoma was reported from Boston 1, total, 1.

Trichinosis was reported from Boston 1, Fall River, 1, Pittsfield, 1, Springfield, 1, Stoneham, 1, total, 5.

Tularemia was reported from Duxbury 1, Wareham, 1, total, 2.

Typhoid fever was reported from Boston 1, Grafton 1, total, 2.

Undulant fever was reported from Boston, 1, Chicopee, 1, Gardner, 1, Haverhill, 1, Holyoke, 1, Lexington, 1, Melrose, 1, total, 7.

## MISCELLANY

### NOTE

Dr. Erich Lindemann, formerly associate in psychiatry at Harvard Medical School, was recently appointed to the Harvard University Faculty of Arts and Sciences to broaden the scope of the new Department of Social Relations. He will continue as a member of the staff of Massachusetts General Hospital. Dr. Lindemann will concern himself with the study of psychologic disturbances of the individual, with special reference to the role of his social relations as a cause of disturbance and as a source of therapeutic aid. His courses will include dynamic psychology and clinical problems in psychologic medicine. In joining the Department of Social Relations which was established last year, Dr. Lindemann will associate himself with sociologists, psychologists and anthropologists. The new Department was formed to break down the limitations of individual departments in working on common problems of social relations.

Dr. Lindemann's research has included experiments in the use of narcosis in treating mental disorders and an original study of the psychiatry of grief, which followed the Coconut Grove fire in Boston.

Dr. Lindemann received his Ph.D. degree in Psychology from Marburg University in 1922 and his M.D. degree from Cologne University in 1926. He came to the United States in 1927. He was a research fellow at Iowa State University from 1927 to 1929, afterward serving as instructor in psychology and psychiatry (1929-1931), assistant professor of psychiatry (1931-1935), and assistant professor of psychology (1932-1935). He was research fellow in neurology and psychiatry at the Harvard Medical School from 1935 to 1937 and was instructor in psychiatry (1937-1941) and associate in psychiatry from 1941 until his present appointment. He also served as instructor in psychiatry, Harvard School of Public Health.

Hospital positions held by Dr. Lindemann include assistant psychiatrist and chief, Psychiatric Out Patient Department, Iowa Psychopathic Hospital (1931-1935), student mental hygiene adviser (1933-1935), associate psychiatrist (1937) and psychiatrist (1943), Massachusetts General Hospital, physician-in-charge, Psychiatric Out Patient Department (1937) and consulting psychiatrist, Massachusetts Eye and Ear Infirmary (1941).

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*The Postnatal Development of the Human Cerebral Cortex* By J. LeRoy Conel, A.M., Ph.D., professor of anatomy, Boston University School of Medicine, and research associate in pathology, Harvard Medical School. Children's Hospital and Infants' Hospital, Boston. Volume I, 104 pp., 98 plates. Volume II, 136 pp., 103 plates. Volume III, 158 pp., 104 plates. Cambridge, Harvard University Press, 1939-1946. Volumes I and II \$3.00 each. Volume III \$12.50.

*The Ranks of Death A medical history of the conquest of America* By P M Ashburn, M D Edited by Frank D Ashburn 8°, cloth, 298 pp New York Coward-McCann, Incorporated, 1947 \$5 00

*The Development of Inhalation Anesthesia With special reference to the years 1846-1900* By Barbara M Duncum, D Phil (Oxon), member of the Nuffield Department of Anaesthetics, University of Oxford Publications of the Wellcome Historical Museum 8°, cloth, with 161 illustrations New York Oxford University Press, 1947 \$12 00

*Human Genetics* By Reginald Ruggles Gates, Ph D, D Sc, LL D 8°, cloth, two volumes, 1518 pp, with 325 illustrations New York Macmillan Company, 1946 \$15 00

*Handbook of Correctional Psychology* Edited by Robert M Lindner, M D, and Robert V Seliger, M D 8°, cloth, 691 pp New York Philosophical Library, 1947 \$10 00

*Rh Its relation to congenital hemolytic disease and to intra-group transfusion reactions* By Edith L Potter, M D, Ph D, assistant professor of pathology, Department of Obstetrics and Gynecology, University of Chicago, and Chicago Lying-in Hospital 8°, cloth, 344 pp, with 65 illustrations Chicago Year Book Publishers, Incorporated, 1947 \$5 50

*The Self You Have to Live with* By Winfred Rhoades Revised edition 8°, cloth, 254 pp Philadelphia J B Lippincott Company, 1947 \$2 00

*Diseases of the Chest, with Emphasis on X-ray Diagnosis* By Eli H Rubin, M D, attending physician, Division of Pulmonary Diseases, Montefiore Hospital and County Sanatorium, New York City, and visiting physician in tuberculosis and physician-in-charge, Chest Clinic, Morrisania City Hospital, New York City With a section, "The Principles of Surgical Treatment," by Morris Rubin, M D, assistant visiting surgeon, Triboro Hospital and Morrisania City Hospital, New York City 4°, cloth, 685 pp, with 355 illustrations and 24 color plates Philadelphia W B Saunders Company, 1947 \$12 00

*Studies and Essays in the History of Science and Learning* Dedicated to George Sarton, on the occasion of his sixtieth birthday Edited by M F Ashley Montague 8°, cloth, 597 pp, with portrait and 38 illustrations New York Henry Schuman, 1947 \$12 00

*Gastritis* By Rudolf Schindler, M D, clinical professor of internal medicine (gastroenterology), College of Medical Evangelists, Los Angeles, senior member of attending staff, Los Angeles County Hospital, consultant in gastroenterology, Birmingham General Hospital, Veterans Administration, Van Nuys, California, and Cedars of Lebanon Hospital, Los Angeles 8°, cloth, 462 pp, with 96 plates New York Grune and Stratton, 1947 \$10 00

*Encyclopedia of Endocrinology* Section IV Ovary Volume VII (two volumes), ovarian tumors and bibliography By Hans Selye, M D, Ph D (Prague), D Sc (McGill), F R S (Canada), professor and director, Institute of Experimental Medicine and Surgery, University of Montreal 4°, cloth, 289, 427, 60 pp, with 38 plates Montreal Richardson, Bond and Wright, 1946 \$21 75

*The Psychoanalytic Study of the Child* Volume II 8°, cloth, 424 pp New York International Universities Press, 1947 \$7 50

*Curare Its history, nature and clinical use* By A R McIntyre, Ph D, M D, professor of physiology and pharmacology, University of Nebraska College of Medicine 8°, cloth, 240 pp, with 23 illustrations Chicago, Illinois University of Chicago Press, 1947 \$5 00

*A History of The American Medical Association 1847 to 1947* By Morris Fishbein, M D With Biographies of the presidents of the Association by Walter L Bierring, M D, and with histories of the publications, councils, bureaus and other official bodies 4°, cloth, 1226 pp, illustrated Philadelphia W B Saunders Company, 1947 \$10 00

*The Physical Background of Perception The Waynflete lectures delivered in the College of St Mary Magdalen, Oxford, in the Hilary Term 1946* By E D Adrian, O M, F R S 8°, cloth, 95 pp, with 21 illustrations New York Oxford University Press, 1947 \$3 25

*The Development of Modern Medicine An interpretation of the social and scientific factors involved* By Richard Harrison Shryock 8°, cloth, 457 pp, with 9 plates New York Alfred A Knopf, 1947 \$5 00

## NOTICES

### ASSOCIATION OF MILITARY SURGEONS OF THE UNITED STATES

The annual meeting of the Association of Military Surgeons of the United States will be held at the Hotel Statler, Boston, from November 13 to 15, inclusive. An unusual program is being offered, with special emphasis on many interesting features developed during the war and since V-J day. Technical information and findings not hitherto generally published will be released by high-ranking representatives of the Army, Navy and Air Force. Speakers from the United States Public Health Service and the Veterans Administration will also participate in this meeting.

All interested physicians are invited.

### BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

A joint meeting of the Boston Society of Psychiatry and Neurology and the New England Pathological Society will be held at the Boston Medical Library, 8 Fenway, Boston, on Thursday, November 20, at 8 15 Dr J W Kernohan will speak on "Secondary Changes Produced by Expanding Intracranial Lesions."

### SOCIETY MEETINGS AND CONFERENCES

#### CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, NOVEMBER 13

##### FRIDAY, NOVEMBER 14

\*10 00 a m -12 00 m Medical Staff Rounds Peter Bent Brigham Hospital  
12 00 m -1 00 p m Clinicopathological Conference (Boston Floating Hospital) Joseph H Pratt Diagnostic Hospital

##### MONDAY, NOVEMBER 17

\*12 15-1 15 p m Clinicopathological Conference. Peter Bent Brigham Hospital

##### TUESDAY, NOVEMBER 18

\*12 15-1 15 p m Clinicorontgenological Conference Peter Bent Brigham Hospital

##### WEDNESDAY, NOVEMBER 19

\*12 00 m Grand Rounds and Clinicopathological Conference (Children's Hospital) Amphitheater, Peter Bent Brigham Hospital  
\*2 00-3 00 p m Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital

\*Open to the medical profession

(Notices continued on page xv)

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## MEDICAL GROUP PRACTICE IN THE UNITED STATES\*

### II Survey of Five Groups in New England and the Middle Atlantic States

G HALSEY HUNT, M.D.,† AND MARCUS GOLDSTEIN, Ph.D.‡

**T**HIS is the second of a series of reports on the purposes and findings of a study of medical group practice conducted by the United States Public Health Service.

During the first eight months of 1946, techniques for the study of group-practice units were worked out and tested in studies of five groups in New England and the Middle Atlantic states. The general method of study, outlined in the first paper of this series,<sup>1</sup> involves approaches by two techniques: an intensive interview survey of the physicians and key administrative personnel of the group, and a statistical analysis of a random sample of the group's medical records. The present paper is concerned only with the development, application and results of the interview survey. Studies are being continued in other parts of the country, and will be the subject of future reports.

#### METHOD OF STUDY

For the study of the first group, comprehensive interview outlines were worked out to obtain detailed information about the group's professional and administrative practices, facilities and personnel, including biographical data on the individual members, and to carry out an opinion survey of the physicians. Interview outlines previously used by Roberts<sup>2</sup> were rearranged and amplified to form the basis of the schedules dealing with the practices of the group as a whole. After the first study, the schedules were revised somewhat and were used for two other groups. Further revision was then found to be necessary, and the resulting schedules were employed with the last two groups. No other major revisions are contemplated for the duration of this study. In the present report, comparable data for all five groups have been used, unless a specific note to the contrary has been made.

The study can of course be conducted only with the full permission and co-operation of the group being studied. The interview survey is carried out

by an analyst familiar with medical practices, who spends two or three weeks with each group. Information regarding administrative and fiscal practices, personnel and facilities are obtained by the analyst from the principal medical and nonmedical administrators of the group. An effort is made to interview each physician and to obtain his opinions on group practice, as well as details of his training and experience.

Because of the lack of factual knowledge about groups and group practice generally, the interview outlines go into considerable detail concerning all aspects of the personnel, organization and practices of groups, consideration of the incomes of individual physicians alone being omitted. It is hoped that by analysis of this mass of detailed information, the common patterns and the variations of organization and practices may be determined.

The data given below, which were selected from the available material either on the basis of known or assumed intrinsic importance or on that of variation among the five groups studied, are primarily presented as illustrations of the kind of information sought in the study and are not necessarily indicative of the nature of group practice in general. The findings are discussed under the following headings: organization, facilities, scope and type of services, professional standards, financial arrangements, volume of work in 1945 and opinion.

#### ORGANIZATION

The great majority of medical groups in the United States are private partnerships, but there are also substantial numbers of hospital groups, industrial groups and consumer-sponsored groups. The classes considered in this report fall into three of these four categories. No consumer-sponsored group was studied in the New England and Middle Atlantic States. Two of the groups are private partnerships, two are hospital groups, with ownership and authority vested in a nonprofit community hospital, and one is an industrial group, with ownership and authority vested in an industrial company. In the last group, the employees and their

\*From the Division of Public Health Methods, United States Public Health Service.

†Senior Surgeon, United States Public Health Service.

‡Public health administrator.

dependents make up the total patient load. All five groups have existed for many years, the period of existence as groups ranging from seventeen to thirty years.

### FACILITIES

The study schedules go into detail about the physical facilities, equipment and hospitals used by each group, but in view of the small number of groups in this series, discussion is limited to a brief consideration of the offices and hospital facilities.

*Offices* Each of the two hospital groups has its offices in the hospital building. One of the partnership groups owns its building, and the other has transferred its clinic-building title to the hospital with which it is integrally affiliated. The industrial group uses two main buildings and two annexes, all owned by the company and located in the adjacent cities in which the company has its plants.

*Hospital facilities* The members of the hospital groups make up the complete staffs of their respective hospitals. Of the two private partnership groups, one is integrally affiliated with a hospital and comprises its complete staff, whereas members of the other group are on the staff of a local community hospital but do not control its professional policies. The industrial group is closely associated with a community hospital with which all its full-time members have staff affiliations, the group controls to a large extent the professional policies of the hospital.

The hospitals range in size from 95 to 374 beds. All the hospitals are registered with the American Medical Association, and all are approved by the American College of Surgeons. Four of the five are approved for intern and resident training by the American Medical Association.

### SCOPE AND TYPE OF SERVICES

The scope and type of services offered by a group are related to its size, the fields of medicine covered by its staff, the variety of ancillary services furnished, the medical requirements of the group's clientele and, possibly most important, the orientation of the group toward either general medical care or specialized work for referred patients.

#### *Primary Activity*

A classification of medical groups according to the type of medical services offered was presented in the introductory paper.<sup>1</sup> A service group is one in which the principal activity is the furnishing of complete medical care to a continuing clientele, whereas a reference group primarily furnishes specialized care to patients referred to them by outside physicians, usually for a single episode of illness. According to this classification, three of the present groups (one private, one hospital and one industrial) are service groups, and two (one private and one hospital) are reference groups. It was noted in the

previous paper that this classification is not absolute, but merely serves to define the principal function of the group. A mixture of activity was found in all the present groups except the industrial group, which is purely service in type. The other two service groups, especially the hospital service group, do a certain amount of referred work, and the two reference groups furnish a certain amount of general medical care. It may be pointed out again that a service group may be composed entirely of specialists. The distinction between service and reference groups is based on a determination of whether the group *as a group* is primarily acting as a "general practitioner" or as a "specialist."

#### *Size of Groups and Fields of Medicine Covered*

The five groups range in size from 15 to 46 members and are therefore larger than most groups in the United States.\* Of the 122 members, 24 per cent are on a part-time basis. More than four fifths of these are in the industrial group. (Over half the membership of this group is part-time, it should be noted that the group classifies a number of men as part-time because they have the privilege of evening private practice, although they actually put in a full day's work with the group.) In the two groups providing psychiatric services, the psychiatrist is a part-time member. These figures, as well as the fields of medical practice covered by each group and the number of physicians in each field, are summarized in Table 1.

In addition to the medical services noted, all the groups provide physiotherapy, and all have clinical laboratories, although the clinical laboratories in one group are operated by the associated hospital and directed by a pathologist who is not a member of the group. Ambulance service is furnished directly only by the two hospital groups. One reference group offers oral surgery, and the industrial group provides general dentistry, including orthodontia. All the groups except one private service group have pharmacies. Only the industrial group affords specific social service.

All but one of the groups provide office, home and hospital care. The one exception, a hospital reference group, does not make home calls.

The two hospital groups have no evening or Sunday office hours for outpatients. The industrial group holds clinic hours between 8:00 a.m. and 6:00 p.m., six days a week. Both private groups have evening office hours, until 8 o'clock in one and until 9 in the other, and patients are also seen on Sunday by these two groups—regularly by one group and occasionally by the other.

An appointment schedule is rather closely adhered to in three of the groups. One of the hospital groups

\*According to the report of the American Medical Association<sup>2</sup> in 1940 only 5.4 per cent of groups in the United States had 15 or more physician members in 1939. A questionnaire survey conducted by the Division of Public Health Methods in the summer of 1946, a report of which is in preparation, showed that about 10 per cent of the groups now have 15 or more full-time physician members.

does not follow an appointment schedule closely, and the industrial group makes appointments only for patients seeing specialists

### Communities Served

The four nonindustrial groups are located in comparatively small communities — three in places of 7000 population or less, and the other in a town of 16,000. The two reference groups draw most of their patients from within a radius of about 50 miles and thus serve estimated populations of 88,000 and 350,000 respectively. The two nonindustrial service groups draw patients from estimated populations of 65,000 and 87,000, respectively, whereas the industrial service group cares for about 50,000 employees

light on the situation. These include the age, training and experience of individual members of groups, membership in a county medical society and certification of specialists by American specialty boards and membership in recognized specialist societies. Concerning the group as a whole, consideration was given to the kind and amount of professional supervision, medical staff meetings, responsibility for patients, system of medical records employed, qualifications required of new members and requirements for postgraduate study.

### Age and Years in Medical Practice

Of the 109 physicians about whom data were available, the average is forty-two and a half years of age,

TABLE 1 Distribution of Members in Five Medical Groups according to Specialty

GROUP	TOTAL MEM BERS	PART TIME MEM BERS	MEDICINE							SURGERY						EYE, EAR, NOSE AND THROAT			OBSTETRICS AND GYNECOLOGY		OTHER SPECIALISTS							
			TOTAL	GENERAL	INTERNAL	DERMATOLOGY	PSYCHIATRY	ALLERGY	INDUSTRIAL	TOTAL	GENERAL	UROLOGY	ORTHOPEDIC	THORACIC	PLASTIC	NEUROLOGIC	TOTAL	COMBINED	EYE	EAR	NOSE AND THROAT	TOTAL	COMBINED	OBSTETRICS	PEDIATRICS	RADIOLOGY	PHYSIOLOGY	DENTISTRY
A	18	—	2	—	2	—	—	—	—	6	4	1	1	—	—	—	3	—	1	2	2	1	1	1	1	1	1	—
B	23	1	7	—	6	—	1*	—	—	7	1	2	1	1	1	—	2	—	1	1	2	2	1	1	2	2	1	—
C	20	3	6	—	4	1	1*	—	—	5	4	1*	—	—	—	—	3	—	2*	1	2	2	1	—	2	1	1	—
D	46	24	19	14†	2	1*	—	1*	1	7	5†	1*	—	1*	—	—	4	1*	1*	2*	3	1*	2*	—	2*	1*	1	2†
E	15	1	5	—	5	—	—	—	—	2	2	—	—	—	—	—	2	—	1*	1	1	1	—	2	1	—	—	1
Total	122	—	39	14	19	2	2	1	1	27	16	5	2	2	1	1	14	1	6	7	10	6	4	—	9	6	1	4
Part Time	—	29	12	8	—	1	2	1	—	6	3	2	—	1	—	—	5	1	3	1	2	1	1	—	1	1	—	2

\*One part-time member.

†Laboratories are in the associated hospital and are directed by a pathologist who is not a member of the group.

‡Not a doctor of medicine.

§Eight part-time members.

||Three part-time members.

|||Two part-time members.

and dependents, living in three contiguous cities and adjacent towns.

The two hospital groups, one reference and one service, both care for predominantly rural populations. The area served by one of the partnership groups (reference) is largely rural in character, and that of the other partnership group (service) is mainly urban and suburban. The clientele of each of the four nonindustrial groups is said to be representative of the population of the area served.

### PROFESSIONAL STANDARDS

One of the obviously important questions about group practice is the professional caliber of the participating physicians. This is not susceptible of accurate measurement or of comparison with the caliber of individual practitioners, but a number of criteria have been used in an effort to throw some

light on the situation. These include the age, training and experience of individual members of groups, membership in a county medical society and certification of specialists by American specialty boards and membership in recognized specialist societies. Concerning the group as a whole, consideration was given to the kind and amount of professional supervision, medical staff meetings, responsibility for patients, system of medical records employed, qualifications required of new members and requirements for postgraduate study.

The total period of internship and residency, as well as the years in medical practice and the types of practice engaged in, is summarized in Table 2. Only physicians for whom complete information was available in these respects are included in the tabulation.

The average number of years since graduation from medical school is almost identical with Rorem's<sup>4</sup> finding of an average of sixteen years since graduation for 415 physicians in 46 clinics.

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the simplest work in any of the various specialties, becoming essentially an uncertified internist, or should he develop interest and skill in one or more specialties, becoming a partial specialist in surgery or obstetrics or some other field, with general practice as his secondary interest? These wide variations in the functions of a general practitioner, which are confusing enough in individual practice, become doubly so when an attempt is made to evaluate the place of the general practitioner in group practice.

At least four concepts are included under the term "general practitioner" as it is commonly employed, and it is important that the term be defined with sufficient accuracy for the reader to determine which concept is meant. These four concepts can be described as follows:

The physician who limits his practice to the field of internal medicine, who considers the patient as a whole individual, but who does not attempt to do any work in surgery, obstetrics or other specialized fields. As noted above, this type of "general practitioner" is essentially an uncertified internist.

The physician who treats the patient as a whole individual and who, in addition to covering the general field of internal medicine, undertakes work in surgery, obstetrics and other fields, within the limits of his training, skill, self-assurance and hospital facilities. This concept is probably most frequently in mind when the unqualified terms "general practitioner" and "old family physician" are used. It is also the kind of general practitioner who seems to be most out of place in group practice, which is usually regarded as a way of escape from the impossible task of trying to know everything about all fields of medicine.

The physician who does some work in the general field of internal medicine, who treats the patient as a whole individual but who has also developed interest and skill in an outside specialty, such as surgery. He therefore becomes a partial (often, eventually, a complete) specialist, paying less and less attention to general practice.

The physician who develops an intimate knowledge of his patients, treating them as whole individuals, but who does not attempt to treat them for any illness that falls outside his own field. This is essentially the concept of "personal physician," and can really be applied to specialists as well as to general practitioners. An eminent internist, certified in internal medicine and in gastroenterology, recently stated that he was a "general practitioner." Further discussion showed that he was using this fourth concept, and when the other concepts were outlined, he said "That sort of thing has no place in the future practice of medicine."

Precision in terminology is desirable, although probably not attainable at this late date, but an effort will be made in these reports to indicate which concept of the general practitioner is being discussed. The concepts described above may be indicated as follows: general practitioner (uncertified internist), general practitioner (multiple field), partial specialist, and personal physician—it should again be noted that a "personal physician" may be a specialist, an internist or even a full-time practitioner of one of the surgical specialties, he may think of, and treat, the patient as a whole individual and still refer the patient to someone else for the diagnosis and treatment of illnesses that fall outside his own specialty.

All four of the nonindustrial groups included in the present report have apparently decided that their organizations have no place for general practitioners of any description, all the physicians in these groups claim to be specialists and state that they limit their practice to their specialties. The industrial group contains 14 general practitioners, who seem in general to fall into the category of "uncertified internist." Of the 103 physicians in all five groups about whom information is available, therefore, 86 per cent limit their practice to one field of medicine (Table 3).

Of the 89 physicians who claim to be specialists, 57.3 per cent are certified by American specialty boards. Fifteen of the nonaccredited specialists are members of specialist societies, so that 74.2 per cent of the specialists are either certified or are members of specialist societies. There is no appreciable difference in this respect between the service and the reference groups.

The specialists in the hospital groups have the highest percentage of certification—66.7 per cent. The figure for the private partnership groups is 57.5 per cent, and that for the industrial group 42.1 per cent.

The specialists forty years of age and over have a higher percentage of certification than those under forty, but it may be noted that all the uncertified specialists under forty about whom information is available have applied for certification, whereas only 17 per cent of the uncertified specialists over forty have applied.

The three hospitals of which the groups form the complete staffs have authority to train physicians for one or more specialty boards.

#### Professional Supervision

It seems obvious that if a medical group is to continue functioning as an organized entity, some degree of professional supervision must be necessary, but only three of the groups reported that there was any direct supervision, even of the younger members. The director of one of the other groups believed that sufficient supervision of the members was attained at staff meetings during discussion of case reports,



whereas the fifth reported that there was no official attempt at supervision. In the opinion survey, 74 per cent of 84 physicians considered professional supervision, direct or indirect, to be desirable, whereas only 46 per cent of these physicians believed that there was any supervision of their own practice.

No special correlation between age and attitude is evident in this question of professional supervision, nor is there any marked distinction between service and reference groups.

### Medical Staff Meetings

Staff meetings of the whole group are held regularly in each of the five groups. The frequency of these meetings varies from once a week to once a month. Case reports are common to all such meet-

would co-ordinate and interpret to the patient the findings of other specialists to whom he might be referred. The same four groups in which the patient is the responsibility of a single physician in a given illness report that their patients, as a matter of policy and as a general rule, have personal physicians within the group membership. This relation is permitted in the fifth group if the patient expressly desires it. In all groups, the personal physician is ordinarily selected by the patients concerned.

This question was also covered in the opinion survey, the physicians being asked whether they considered it medically desirable for each patient to have a personal physician. Of 83 physicians, 76 per cent replied in the affirmative and 22 per cent in the

TABLE 3 Status of Specialist Certification of Physicians in Five Medical Groups

CLASSIFICATION	TOTAL	PHYSICIANS CERTIFIED	NO OF	PHYSICIANS WHO	UNCERTIFIED
	NO OF	BY AMERICAN	UNCERTIFIED	HAVE APPLIED FOR	PHYSICIANS WHO
	PHYSICIANS	SPECIALTY BOARD	PHYSICIANS*	CERTIFICATION	ARE MEMBERS OF
					SPECIALIST SOCIETIES
		NO	PER-	NO	PER-
			CENTAGE		CENTAGE
				PER-	
				CENTAGE OF	
				UNCERTIFIED	
				PHYSICIANS*	
Practice not limited to specialty	14	—	—	14	14 2
Practice limited to specialty	89	51	57 3	20	40 5
Full time	73	41	56 2	18	38 7
Part time	16	10	42 5	2	50 0
Service group	51	29	56 9	9	42 9
Reference group	38	22	57 9	11	37 5
Private organization	40	23	57 5	10	31 3
Hospital organization	30	20	66 7	7	50 0
Industrial organization	19	8	42 1	3	45 5
Physicians under forty years of age	35	17	48 6	17	16 7
Physicians forty years and over	54	34	63 0	3	63 2
Totals	103	51	—	21	17
Averages			49 5		33 3

\*There were 3 uncertified physicians from whom information about application for certification was not obtained, and who are therefore omitted from the number of uncertified physicians in the calculation of percentages.

†There was 1 uncertified physician from whom information about society membership was not obtained, and who was therefore omitted from the number of uncertified physicians in the calculation of percentages.

‡This general practitioner has applied for certification in internal medicine.

ings, death reports are considered by four of the groups, and special reports by staff members and a journal club are parts of the programs in two

### Responsibility for Patients

In all but one of the groups — a hospital service group — the patient is primarily the responsibility of a single physician during a given episode of illness. In that group there is, in general, departmental rather than individual responsibility.

In the groups in which the patient is primarily the responsibility of a single physician, selection is usually made by the patient, although a referring physician outside the group may, in two groups, request the services of a particular physician. In three groups, a patient who has no preference is usually assigned to an individual physician by a nonmedical admitting officer.

There has been considerable discussion of the place of the "personal physician" in group practice — that is, one who would develop an intimate physician-patient relation with the patient and who

negative, 2 per cent were noncommittal. Three of the groups were almost unanimous in favor of the personal physician relation in group practice, about two thirds of the fourth (a hospital service group) replied affirmatively, and the fifth group (a hospital reference group) had a majority (9 of 16 members) who considered it medically inadvisable or unnecessary for each patient to have a personal physician. Interestingly enough, this was not the group that has departmental rather than individual responsibility for the patients.

Among 48 physicians in four groups who thought that each patient should have a personal physician, 29 would permit the patient to choose any member of the group. Fourteen physicians believed that the personal physician should be chosen from among the general practitioners, and 5 that he should be chosen from among the internists of the group, although one of these wished to exclude physicians in the medical subspecialties.

There was no particular difference in attitude between service and reference groups concerning re-

sponsibility for the patient. The age of the physicians questioned also had no bearing on this point.

### *Medical Records*

It is implicit in the hospital-standardization program of the American College of Surgeons that a good system of medical records (both well designed and well kept up) is essential to the operation of a first-class hospital. Outpatient records cannot be expected to attain the same standards of completeness required of hospital records, but in view of the fact that patients of a medical group are often seen by more than one physician, it seems reasonable to expect that groups should keep more complete medical records than most individual practitioners do. Clark and Clark<sup>6</sup> state that the essence of group work is the co-ordination of the various departments and that experience has demonstrated that the quality of the medical records in a group-practice organization reflects with remarkable accuracy the degree of co-ordination it has achieved. This statement has been taken as a working hypothesis in both the interview study and the record study, subject to confirmation or revision by the accumulation of data.

As part of the interview survey, the medical-record librarian is interviewed, and detailed information is obtained about all aspects of the record system. An attempt is also made to evaluate the extent to which the system is followed in actual operation.

It should be noted that all the groups studied were (or recently had been) shorthanded because of the war, both in physicians and in clerical help, and that all of them commented that their records at the time of the study were less well kept than before the war, all were hoping to improve the keeping of medical records when the manpower shortage became less acute.

Probably the most important single question about the systems of medical records used by groups is whether the records are kept in a unified form, with all physicians who see a patient having access to and making entries in the same record. A second question of significance is the relation of the hospital records of hospitalized patients to the outpatient records. The data presented below relate only to these two points and do not include consideration of such details of record keeping as diagnostic nomenclature, arrangement of records, filing systems and completeness with which the records are kept. Some of these factors are considered more fully in a future record study, which will be reported separately.

All four nonindustrial groups have unified systems of medical records. In the three groups that are integrally affiliated with hospitals, there is a true unit system, the clinic and hospital records of each patient being filed together in a single folder under one unit number. The fourth group has a unified record system for patients seen in the office or at home, with all such visits of a given patient recorded on the same form. In the industrial group, each family is assigned

a number on the first visit of the worker or one of his dependents, but each department, in each of the two clinics that this group operates, may keep its own file of records, so that the record of a given patient may be kept and filed in several scattered fragments.

It has already been noted that three groups maintain an integral hospital-clinic unit record system of hospital records. The other groups usually enter a short note on the clinical record that the patient has been hospitalized, but as a rule few details of the patient's treatment or course are included.

### *Qualifications for New Members*

Information on the question of qualification was obtained from two groups. In one, a hospital service group, all new members must be certified specialists. In the other group, also a service group, a general practitioner is required to have had more than one year of hospital training, and a specialist must have the full qualifications for an American specialty board, but need not actually possess a board certificate.

### *Postgraduate Study*

Although only one group specifically required younger men to take formal postgraduate study in 1944 and 1945, all encouraged such studies. A member of one of the groups was given leave of absence with pay for a full year to continue studies in orthopedic surgery, and another physician had spent several weeks in postgraduate study. A number of physicians had taken, or were taking at the time of the study, shorter postgraduate courses. Visits to outside medical centers, often referred to as "clinic trips," were more frequent than formal postgraduate work, but were not a definite requirement in any group.

## FINANCIAL ARRANGEMENTS

### *Source of Income*

All but one of the group depend principally on fees-for-service for their income. The exception is the industrial group, which is entirely supported by the sponsoring corporation. In all the fee-for-service groups, charges are said to be comparable with those made by local individual practitioners. Charges are adjusted to the patient's ability to pay, although in only one group is this ability formally investigated. In three groups the ability of the patient to pay a specified fee is determined initially by the business-office personnel, whereas the patient's physician makes this determination in the fourth group. Any question concerning a medical bill is resolved by the business manager in one group, and by the physician involved (if necessary, in conjunction with the medical director) in the other three. In one hospital group the fee schedule is publicly listed.

### *Distribution of Income*

From the point of view of the physicians who practice in groups, the problem of income distribution is of fundamental importance, since on its satisfactory solution depend to a considerable extent the morale of the members, the avoidance of internal friction and even the continued existence of the group. Furthermore, the method of income distribution may influence the type of medical care given — the most obvious example is the effect on intragroup consultations. Some of these methods place a premium on the extensive use of consultations, whereas others tend to penalize the use of consultations and place a premium on one member's keeping and treating a patient as long as possible. The ideal income arrangement should be such as to encourage the liberal use of consultations when indicated but not to place a premium on unnecessary consultations.

Examples of three methods of income distribution are furnished by these five groups, although it should be noted that none of them use what is probably the commonest method — that is, payment to each member of a specified percentage of the total net income of the group, which may be determined annually or may depend on point scores attained by members during the year.

The two private groups differ in their arrangements for sharing the net group income. In one, the income is divided among the members according to the money value of the work done by each department. In the other, each member of the group, whether partner or employed associate, is paid a salary, which varies according to a number of factors. The surplus net income is then divided into equal shares among the partners, each senior partner receiving a full share and each junior partner a half share. In both hospital groups and in the industrial group, all the physicians are paid salaries that are fixed annually. Training, experience, competence and length of time with the group all contribute to the salary determination in the four groups in which the salary is paid. In one of these groups, account is also taken of the money value of the work done by the various departments during the preceding year.

In the opinion survey, all 13 members of one private group expressed a preference for a salary in addition to share, whereas 14 of the 16 members of the other private group preferred a straight percentage distribution. Two members of this group regarded a fixed salary as preferable. There was lack of agreement on this question among the three groups whose members are paid on a fixed-salary basis: in one, all the members considered a fixed salary to be the preferable type of income distribution, whereas a majority of the other two groups (12 of 19 members, and 7 of 12 members) believed that payment should be on the basis of salary in addition to share.

### *Fiscal Analysis*

Since figures were obtained as confidential information, it is not possible to publish any analysis of the actual magnitude of income and expenditures. A few words may be said, however, regarding the proportion of gross income distributed to physicians, which was ascertained for three of these groups. In the hospital groups, the percentage relation between the amount paid to the physicians and the amount received by the hospital for professional services was considered to be the percentage of gross income distributed to the physicians. In the three groups from which this information was obtained, the percentages distributed to the physicians were 61.2, 67.3 and 72.1. It may be noted that Rorem,<sup>4</sup> in studying twelve clinics in 1930, found distribution percentages ranging from 54.6 to 72.2, and that a poll in 1944, covering over 5000 physicians throughout the country, showed an average ratio of net income to gross income of 63.9 per cent.<sup>6</sup>

### *VOLUME OF WORK IN 1945*

Volume figures are difficult to get and even more difficult to interpret, since groups vary widely both in the type of figures that they keep and in the completeness with which they keep them. It has been found, in other groups as well as in the five reported herein, that the annual number of new patients seen and the total annual number of clinic visits are almost always obtainable. The number of actual patients seen in a year is almost never obtainable, and in many cases the total number of clinic visits is not differentiated to show the number of visits to physicians and the number of visits (for x-ray examination, laboratory study, physiotherapy and injection by nurses) on which the patients were not seen by physicians. Records of home calls are likely to be incompletely kept, and in the groups without integral hospital affiliation, the statistics concerning hospitalized patients are often incomplete.

In an attempt to estimate patient load per physician, a further complication is caused by the fact that the present figures relate to 1945, when all the groups had men in or returning from the armed forces. An estimate of the number of physicians practicing with each of the five groups in 1945 was therefore made, the portion of the year during which returning or new members practiced with the group and the estimated fraction of time contributed to the group by part-time members being taken into account (Table 4). These figures, although somewhat arbitrary, are thought to give a reasonably accurate picture of the actual man-years worked in each group in 1945.

A special problem regarding the hospital groups, especially those that do a large volume of referred work, concerns the definition of "new patient." The study was designed to include only outpatients, and in groups not integrally affiliated with hospitals, the

figures obtained ordinarily referred only to outpatients, but the groups associated with hospitals vary in their practices concerning new patients who are hospitalized on their first visits. In one group, practically every patient who is hospitalized is first examined as an outpatient, and this is counted as an outpatient visit. In other groups, patients referred from outside physicians are admitted directly to the hospital and are not counted as having had an outpatient visit. Some of the variations in Table 4 may be related to this factor.

#### Number of Office Visits and Home Calls

Office visits by patients to physicians and the total number of clinic visits are presented in Table 4.

were 6355 home calls in 1945, when the group contained 9 physicians. The specialty reporting most home calls was pediatrics, which averaged 3230 calls per physician. Internal medicine was next, with an average of 1224 calls per physician.

#### Number of New Patients

It is hoped that this figure, interesting in itself as a crude index of volume, and hence of the degree of acceptability of group practice to the public, will also serve as a criterion of the amount of reference work done in a group. One would expect that a purely service group taking care of a continuing clientele, would have a relatively small number of new patients per physician, or per 100 office visits,

TABLE 4. Office Visits, Total Clinic Visits and New Patients in 1945\*

GROUP	TYPE OF GROUP	NO. OF PHYSICIANS	OFFICE VISITS		TOTAL CLINIC VISITS†		NEW PATIENTS				
			NO.	PER PHYSICIAN	NO.	PER PHYSICIAN	NO.	PER PHYSICIAN	PER 100 OFFICE VISITS	PER 100 TOTAL CLINIC VISITS	
A	Reference	16	—	—	56,476	3530	9153	572	—	16.2	
B	Reference	15	19 819	1321	19 819	1321	2698	180	13.6	13.6	
C	Service	9	34 748	3860	50,075	5564	3400	378	9.8	6.8	
D	Service	18	105 921	4884	146 866	8159	—	—	—	—	
E	Service	12	—	—	20 946	1746	2923	244	—	14.0	
Four groups composed entirely of specialists			52	54 567‡	22.4‡	147 316	2831	18,174	350	10.2‡	12.3
All groups			70	160 488§	1275§	294 182	4203	—	—	—	—

\*According to a study conducted by Cioceo and Altman in 1942, the average annual patient load of 265 specialists in Baltimore, 198 in the District of Columbia and 173 in Georgia was respectively 3700, 3485 and 4700.

†Includes office visits to physicians and other visits for x-ray and laboratory study and so forth during which patients were not seen by a physician.

‡Figures from two groups.

§Figures from three groups.

In the three groups in which visits to physicians were distinguished from total clinic visits, the number of visits per physician ranged from 1321 to 5884. Total clinic visits, determined for all five groups, ranged from 1321 to 8159 per physician. Both the office figures in this column (1321 and 1746) were reported by groups integrally affiliated with hospitals and do not reflect the amount of work done for hospitalized patients. In one of these, x-ray and laboratory work is done by the associated hospital, so that the total number of clinic visits is the same as the number of office visits to physicians.

Comparison may be made between the number of office visits per physician in the two groups made up entirely of specialists and the figures obtained by Cioceo and Altman<sup>7</sup> in a study of 636 specialists in Baltimore, the District of Columbia and Georgia. One group reports a much smaller patient load than the Baltimore specialists, whereas the patient load of the other is exceeded only by that of the Georgia specialists.

The industrial group and one of the private service groups were the only ones reporting any appreciable number of home calls. In the latter group, there

and that a purely reference group would have a large percentage of new patients.

This relation does not obtain in the four groups from which new patient figures were obtainable, but it may be pointed out again that three of these groups are integrally affiliated with hospitals, and there is reason to believe that in two, many patients are admitted directly to the hospital and are not included in the tabulation of new patients, although their hospital care actually devolves on the group members. Since hospital admission figures do not ordinarily distinguish between old and new patients, the extent of this under-reporting cannot be determined, but the direct hospital admissions almost certainly confuse the true picture.

#### Volume of Surgery

Comparable figures on volume of surgery were obtained from the three groups associated with hospitals. The totals for all operative procedures in 1945 (except oral surgery) were 4921, 4022 and 1409, respectively, or 547, 619 and 403 operative procedures per active surgeon. In the first and third of these groups, eye, ear, nose and throat operations

were reported separately. If these operations and the corresponding surgeons are omitted, the figures for operative procedures in the two groups become 3615 and 1239, or 603 and 620 per active surgeon.

Volume of Obstetrics

Total deliveries in four groups, including stillbirths, were 1520, or 253 per obstetrician. The volume of obstetrics does not seem to be correlated with the service or reference classification, but the

OPINION

In an effort to determine what the physicians in group practice think of the major controversial points connected with this technic for furnishing medical care, an opinion survey of individual members was carried out. In the first three groups, this was done entirely by interviews, the analyst filling out the schedule form after completion of the interview. Beginning with the fourth group, each mem-

TABLE 5 Advantages of Group Practice as Rated by 84 Physicians in Five Groups \*

ADVANTAGES	RATED BY FIRST THREE GROUPS†		RATED BY LAST TWO GROUPS‡		ALL FIVE GROUPS§		RELATIVE RANK IN FIVE GROUPS
	NO	PER-CENTAGE	NO	PER-CENTAGE	NO	PER-CENTAGE	
Satisfaction of working in atmosphere of professional co-operation	30	62.5	10	27.8	40	47.6	2
Freedom to do one's best work and to obtain laboratory work and consultations without restrictions	13	27.1	22	61.1	35	41.7	3
Professional development stimulated by close professional contact with other members	2	4.2	14	38.9	16	19.0	6
Time for vacations, medical meetings and postgraduate study can be taken without danger of losing patients or income	6	12.5	5	13.9	11	13.1	8
Young physician is kept busy from start so that he does not lose skill acquired during training	3	6.3	2	5.6	5	6.0	10
Young physician makes living income from start	2	4.2	3	8.3	5	6.0	11
Group practice yields larger financial returns to physician, considering career as whole	2	4.2	1	2.8	3	3.6	12
Patients benefit financially either by reduced fees or by getting more medical care for same expenditure	9	18.8	5	13.9	14	16.7	7
Operation of prepayment plans is facilitated	0	—	0	—	0	—	13
Groups provide specialist services for small communities that otherwise could not support them	3	6.3	5	13.9	8	9.5	9
Groups give patients better medical care by providing facilities for easy consultation, formal and informal, and for laboratory work	42	87.5	19	52.8	61	72.6	1
Physician in group is freed from details of business administration	11	22.9	9	25.0	20	23.8	5
Physician has regular daily and weekly working hours with practice covered during time off duty	12	25.0	11	30.6	23	27.4	4

\*The wording of this question in the present interview outlines is as follows: "The following are the chief advantages that have been claimed for group practice. On the basis of your own experience, please check the *three* (no more) most important reasons why you think that group practice is preferable to individual practice (if an advantage that you consider to be one of the three most important is not listed, write it in)." In the first three groups no list was presented; each physician was asked to name the advantages and if more than three were named the first three mentioned were used in the tabulation presented above.

†Included 48 physicians.

‡Included 36 physicians.

§Included 84 physicians.

hospital groups were substantially higher in the number of deliveries per obstetrician than the private partnerships. The ratio for the two hospital groups was 280 deliveries per obstetrician, whereas that for the private partnership groups was 227.

Deaths

Information regarding deaths of hospitalized patients was obtained from four groups, three of which make up the entire hospital staff. The maximum death rate was 4.8 per cent of hospital admissions, and the mean was 3.1 per cent.

Information on autopsies was obtained from the four groups. The autopsy rate ranged from 76 per cent in these four groups, with an

Medical Association requires a minimum autopsy rate of 76 per cent in hospitals approved for internship and residency.

ber has been asked to fill out the form himself, although it has proved most satisfactory to have the analyst present when he does so, to answer any questions of interpretation that may arise. Schedule revisions have also involved considerable rewording of some questions in the interest of clarity and precision. For this reason, the results are not comparable in all respects for all five groups.

The controversial questions considered in the present report are the advantages and disadvantages of group practice, the minimum number of physicians necessary for efficient group practice, and specialties. The results of the opinion survey about other questions are reported above, in the discussions of professional standards and income distribution.

*Advantages and Disadvantages*

A compilation of the principal advantages and disadvantages that have been claimed for group practice was presented in the previous paper<sup>1</sup> During the course of study, changes in the method of approaching this question have seemed necessary. In the first three groups, each member was asked to name the principal advantages and disadvantages, but this technic caused serious difficulty in the analysis of the answers, even when the analysis was limited to the first three answers of each member

must therefore be interpreted cautiously. On several of the items the last two groups differed sharply from the first three, and from the data it cannot be determined whether these differences have real meaning or are related to the change in study technic.

The last two groups rated "freedom to do one's best work and to obtain laboratory work and consultations without restrictions" as the most important advantage of group practice. After this was "groups give their patients better medical care, by providing facilities for easy consultation, formal and

TABLE 6 *Disadvantages of Group Practice as Rated by 37 Physicians in Two Groups\**

DISADVANTAGES†	STRONGLY POSITIVE "TAUK" RATING		WEAKLY POSITIVE "TAUK" RATING		TOTAL POSITIVE "TAUK" RATING		FALSE RATING (ANY DEGREE)		PHYSICIANS NEUTRAL OR WITH NO OPINION	
	NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE
Intimate patient-doctor relation lost in group practice; groups practice impersonal medicine	6	16.2	8	21.6	14	37.8	17	45.9	6	16.2
Physicians' local professional contacts outside group limited (as by close organization of group or by animosity of outside practitioners)	8	21.6	10	27.0	18	48.6	14	37.8	5	13.5
Claimed advantages of close professional co-operation lost because of internal friction	1	2.7	1	2.7	2	5.4	28	75.7	7	18.9
Patient's choice of consultants lost	4	10.9	10	27.0	17	45.9	15	40.5	3	8.1
Patients subjected to unnecessary consultations and laboratory work	2	5.4	3	8.1	11	29.7	22	59.5	4	10.8
Group organization stimulates unethical practices (soliciting advertising press publicity)	0	—	0	—	0	—	31	83.8	6	16.2
General hospitals approved by American College of Surgeons (with regular staff meetings, many specialists and better laboratory and x-ray facilities) more effective than medical groups in stimulating physicians' professional advancement and in providing highest type of medical care for patient‡	10	27.0	1	2.7	11	29.7	16	43.2	10	27.0

\*Both these groups are service groups and the answers recorded apply only to service groups.

†The present schedules contain the following additional item: "Group practice yields smaller financial returns to the well-trained specialist, considering his career as a whole." The two groups reported were not asked to rate this statement.

‡There is some doubt whether all respondents made the desired distinction between groups whether or not they are associated with hospitals and general hospitals not staffed by groups. The wording in the present schedule is: "General hospitals not staffed by groups but approved by the American College of Surgeons, are more effective than medical groups in stimulating the physician's professional advancement and in providing the highest type of medical care for the patient."

beginning with the fourth group, a list of advantages was drawn up, and each member was asked to check the three that he considered most important. A similar list of disadvantages and criticisms was drawn up, but each physician was asked to rate the degree of truth or falsity of each one, on a scale of five (strong and weak positive, neutral or no opinion, weak and strong negative).

The list of advantages presented for rating, in the order in which they are arranged in the schedules, is shown in Table 5. The answers received from the members of the first three groups were fitted as accurately as possible into the present list, the first three advantages mentioned by each physician being used. It is obvious that the first three advantages mentioned by a respondent are not necessarily those that he considers most important, and the results

informal, and for laboratory work," whereas in third place was "professional development stimulated by close professional contact with other members."

The first three groups gave first place to "groups give their patients better medical care and so forth," second place to "satisfaction of working in an atmosphere of professional co-operation" and third place to "freedom to do one's best work and so forth."

Because of the complete change in the technic for recording disadvantages, comparable figures were not obtained from all five groups. The disadvantages most frequently mentioned in the first three groups were as follows: a well-trained specialist makes less money in group practice than in individual practice (mentioned by 29 of 48 physicians), and there is likely to be animosity toward the group

cytic cells were predominantly mature. Relatively few cells of myelocytic stages were noted. There was a marked increase in the percentage of eosinophils. Polymorphonuclear and metamyelocytic stages were present. There was a slight increase in plasma and reticulum cells. Megakaryocytes were present in a fair number, actively producing platelets. The diagnosis was splenic-vein thrombosis.

X-ray examination disclosed no esophageal varices.

Dr. Louis Weissfuse made the following diagnosis and comment:

The diagnosis is splenic-vein thrombosis, with infarction of the spleen. The diagnosis of splenic-vein thrombosis was suggested by Dr. Dameshek on the basis of personal observations. In these cases there was a history of hematemesis since early childhood, splenomegaly after the episode of hemorrhage without the occurrence of cirrhosis of the liver. At autopsy these cases were found to have been due to thrombosis of the splenic vein, with return flow of blood through the vasa brevia of the stomach and with dilatation and subsequent rupture giving rise to the episodes of hematemesis. None of the cases showed any evidence of cirrhosis of the liver. In the patient under discussion all tests revealed the liver function to be perfectly normal. There was no evidence of esophageal varices. The therapy in these cases has thus far been unsuccessful. Splenectomy has been ineffectual in relieving the hematemesis and has frequently given rise to postoperative thrombocytosis and thrombosis of veins throughout the body, with subsequent death.

Dr. Leonard suggested that splenectomy be performed with the use of Dicoumarol to prevent postoperative thrombotic episodes. After consultation with Dr. Dameshek it was decided to perform splenectomy.

The patient was admitted to the Jordan Hospital on January 10, 1947, and operation was performed on January 11. He was given pontocaine-glucose by fractional spinal method supplemented by Pentothal Sodium and nitrous oxide and oxygen. The abdomen was opened through a long left upper paramedian incision. Because of the patient's narrow build this incision was crossed just above the umbilicus by a transverse incision transecting the left rectus muscle and splitting the internal oblique and transversalis muscles. Excellent exposure was obtained.

The lower half of the spleen was found to be replaced by a large unilocular, smooth, symmetrical cyst. Numerous adhesions to the left anterior and lateral walls and to the splenic flexure of the colon were freed manually. The spleen and cyst were easily delivered. The presplenic fold was cut, and the lower portion of the gastrosplenic ligament was clamped, cut and ligated. With the specimen held medially the tail of the pancreas was freed from the hilus, and the splenic vessels were secured individually after opening of the lienorenal ligament. The remainder of the gastrosplenic ligament was clamped and cut, and the specimen removed. All vessels were individually ligated with No. 1 chromic catgut. Through the lesser peritoneal cavity the splenic vein was exposed at the upper border of the pancreas, and no evidence of preoperative thrombosis was noted. The liver was normal to inspection, and no biopsy was taken. The wound was closed in layers with interrupted cotton sutures.

The patient received a transfusion of 500 cc of citrated blood during the operation, and he left the operating room in

excellent condition. The pathological report by Dr. Frank Mayner was as follows:

The specimen consists of a spleen measuring 19 by 10 by 8 cm (Fig. 2 and 3). One pole comprises a large cyst measuring 10 by 10 by 8 cm. The outer surface is smooth. It is filled with semisanguineous fluid. The inner surface is rough, owing to the deposition of coagulated blood. The wall measures less than 0.1 cm in thickness. The cyst wall is intact throughout the specimen and in the portion next to the spleen proper. No communication is found with any part of the spleen. The area nearest the spleen contains coagulated blood. Section of the spleen shows nothing unusual. The organ is firm in consistence and reddish purple, and the malpighian corpuscles are not seen.

Microscopical examination of the cyst reveals a few red cells near and attached to the fibrous tissue lining the thin wall. The wall consists of fibrous tissue measuring in thickness between 15 and 20 cells. Section of the spleen shows prominent sinuses and pulp, which are empty and contain little or no blood. The capsule and trabeculae are normal. The malpighian corpuscles are moderately hyperplastic. The diagnosis is hemorrhagic cyst of the spleen.

The patient had an uneventful convalescence and was discharged from the hospital on the 10th postoperative day. Since discharge he has felt better than he had in years and is gaining weight steadily. He has no more pain and so far has had no complaints. When he was seen on February 28 by Dr. Dameshek, physical examination and blood studies were completely negative.

#### SUMMARY

A case of false cyst of the spleen of the hemorrhagic type is reported. Because of hematemesis a preoperative diagnosis of splenic-vein thrombosis was made. The etiology of the hematemesis could not be explained after thorough study.

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## FAILURE OF THE PERITONEAL-BUTTON OPERATION FOR ASCITES

## Report of Two Cases

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THE surgical treatment of patients with recurrent massive ascites that requires frequent abdominal paracentesis has long been a challenging problem. Operative procedures designed to remedy the defect have carried an appreciable mortality, particularly in patients with portal obstruction due to hepatic cirrhosis who develop ascites relatively late in the course of the disease. Such procedures fall into several well defined groups. Some of these are designed merely to rid the patient of an oppressive volume of fluid, others attempt to eliminate factors in the production of ascitic fluid, and still others attempt to improve the body economy by returning water, electrolytes and protein to the general circulation. To this last group belongs the peritoneal-button operation, in which a flanged glass tube is inserted between the peritoneal cavity and a pocket made in the subcutaneous tissues of the anterior abdominal wall. This has the theoretical advantage of providing a constant slow clysis of the patient's own blood transudate and the practical advantage of being a relatively simple operation that can be done under local anesthesia. Details of this procedure have been described by Crosby and Cooney.<sup>1</sup> This principle has been employed with minor changes in technic and with varying degrees of enthusiasm over a period of years. Tannahill<sup>2</sup> reported the use of such a button in 1930. More recently, with the improved medical management of patients suffering from hepatic insufficiency and with better control of surgical infection, interest in this operation has been revived.

It is the purpose of this paper to report experience with 2 patients who were provided with peritoneal buttons and subsequently subjected to post-mortem examination.

## CASE REPORTS

CASE 1 D V (PBBH A-4732) a 57-year-old Greek kitchen helper with a known diagnosis of portal cirrhosis was admitted to the hospital for operation after a 3½-month period of recurrent ascites. During the month prior to admission this fluid reaccumulated after paracentesis at 10-day intervals to the point of producing respiratory distress. On November 22, 1946, a glass peritoneal button of the Cooney type was inserted. The postoperative course was uneventful and the patient encouragingly developed marked edema of the lower abdominal wall and genitalia. He was discharged from the hospital 15 days later with no evidence of reaccumulation of peritoneal fluid. On December 18, however, less than 1 month after operation fluid had reaccumulated so that he again required paracentesis. During the next 3 months, until the time of death, a total of 46,700 cc. of ascitic fluid was removed from the abdomen at intervals ranging from 1 to 3 weeks. This fluid had a constant specific

gravity of 1.010 with total protein determinations ranging from 0.52 to 0.68 gm. per 100 cc. The serum protein was maintained in the range of 5.9 to 6.6 gm. per 100 cc., with albumin globulin ratios of between 0.3 and 1.0. The patient died on March 23, 1947, after a massive gastrointestinal hemorrhage from the rupture of an esophageal varix.

*Autopsy.* Post mortem examination revealed marked wasting of the upper part of the body, with a prominent abdomen and bulging flanks. Moderate edema of the genitalia was present, but no appreciable edema of the lower abdominal wall or of the lower extremities was noted. There was an 8-cm. inverted curvilinear well healed right rectus skin incision at the level of the umbilicus as well as numerous old and recent midline lower abdominal scars from the paracenteses. The umbilicus was flat, and no caput was seen. On opening of the peritoneal cavity 6500 cc. of cloudy straw-colored fluid was released. The peritoneal surfaces were white smooth shiny and opaque. The deep aspect of the peritoneal button was seen anchored firmly in place, with a silk pursestring suture 5 cm. below and to the right of the umbilicus. The button was free of adhesions, the lumen was patent, and there was no increased peritoneal reaction in its vicinity. A segment of abdominal wall measuring 15 by 12 by 3 cm. was then removed from the right lower quadrant. The subcutaneous tissues appeared identical at the transected superior and inferior margins of the block and measured 1.5 cm. in thickness. A collapsed subcutaneous cystic space measuring 10 by 7 by 4 cm. and communicating with the peritoneal cavity was identified (Fig. 1). This had a smooth white glistening trabeculated surface with numerous shallow diverticulae at its margins. There was a single firm band of scar tissue running from the floor to the roof of the cavity in the vicinity of the button. This lining whose appearance was entirely similar to the previously described peritoneal surface, could be seen arching evenly into the defect provided by the button. The glass button was freely movable within its tract and there was no visible reaction about its flanged neck. The wall of this cavity could be identified as a tough fibrous layer 0.15 cm. in thickness. Beyond it the layers of the abdominal wall were readily defined. A zone of yellow lobular fatty tissue separated the cyst wall on one side from the anterior rectus sheath and on the other from Scarpa's fascia. Microscopical sections taken from the superficial and deep layers of this wall (Fig. 2) presented evidence of an old inflammatory process with formation of a layer of dense poorly vascularized fibrous tissue. There was some scarring of the adjacent fat, with thickening of connective-tissue trabeculae and occasional perivascular foci of mononuclear inflammatory cells. There was a separate thin cellular lining layer composed of flattened elongated, darkly staining cells. Additional findings consisted of a diffusely nodular firm liver weighing 960 gm. histologic examination of which revealed toxic cirrhosis, an engorged spleen weighing 340 gm. and a blood filled upper gastrointestinal tract with a well defined perforation of an esophageal varix.

CASE 2 D B (PBBH A-46-148) a 46-year-old federal employee gave a history of having consumed over a pint of whisky a day for many years. He was admitted to the hospital in August, 1946 with a diagnosis of portal cirrhosis following 4 months of recurrent ascites that required frequent abdominal paracentesis. On August 16, a Cooney type of peritoneal button was inserted. In spite of this procedure fluid continued to accumulate and repeated paracenteses were again necessary. One month after operation 9000 cc. of fluid was removed and 8 days later at the time of death a massive collection of ascitic fluid had again developed. The fluid obtained had a low specific gravity with a total protein of 0.27 gm. per 100 cc. The total serum protein in

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that period varied from 53 to 57 gm per 100 cc, with albumin-globulin ratios of from 0.3 to 0.5. The hospital course was unremittingly downhill, with signs of generalized

the costal margin, and the umbilicus was everted. There was a 9-cm., healed, curvilinear incision, with the convexity downward, located 3 cm. below and to the left of the umbilicus

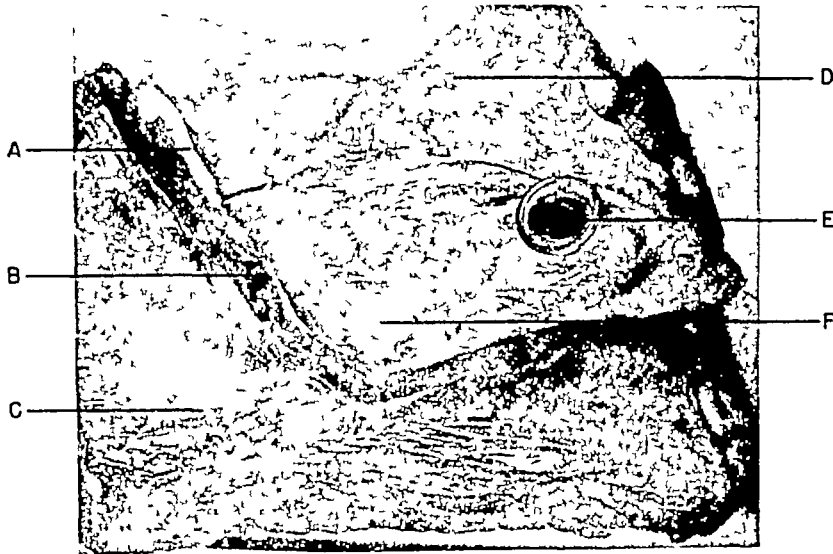


FIGURE 1 Portion of Subcutaneous Space in Case 1

A shows the anterior rectus sheath, B the rectus muscle, C the peritoneum, D subcutaneous tissues, E the superficial aspect of the peritoneal button and F the lining of the cavity

hepatic insufficiency, cholemia and terminal convulsive episodes

*Autopsy* Post-mortem examination disclosed marked pitting edema of the legs, genitalia and body to the level of the

Beneath this skin flap was a circumscribed fluctuant area. On incision of this area, a subcutaneous fluid-filled space lined with a smooth, glistening membrane was encountered. The outline of this cavity was irregular, and there was some

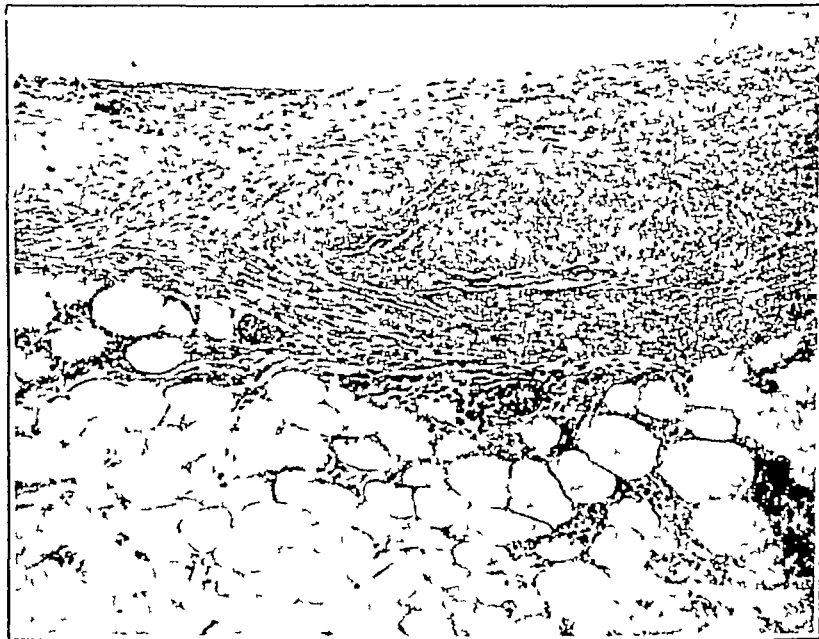


FIGURE 2 Superficial Wall of Cavity in Case 1 ( $\times 100$ )

Note the dense hyalinized connective-tissue layer and the residual inflammatory exudate extending into the adjacent subcutaneous tissues

costal margins. The skin and scleras showed a yellowish discoloration, and there were numerous areas of ecchymosis. The superficial veins were prominent over the lower abdomen, upper chest and arms. The abdomen protruded 9 cm. above

trabeculation at its margins. The cavity measured 4 by 2.5 by 3 cm. The flanged neck of the superficial portion of the button could be seen occupying the central portion of the floor of the space. When the peritoneal cavity was opened,

8600 cc. of thin straw-colored fluid was released. The subcutaneous tissues varied from 0.3 to 1.0 cm in thickness. The peritoneal surfaces were smooth white and glistening but again opaque. The deep portion of the peritoneal button was readily identified. There was no increased peritoneal reaction in its vicinity; no adhesions were found, and the lumen of the button was patent. The peritoneal layer blended evenly with the wall of the canal provided by the button and was continuous with the lining of the subcutaneous space. Additional findings consisted of a firm diffusely nodular liver weighing 1160 gm, a noticeably distended portal vein, a large firm spleen weighing 495 gm, and evidence of the establishment of an elaborate collateral circulation. Microscopical examination of the liver and pancreas revealed extensive deposits of hemosiderin. This finding led to a primary diagnosis of pigment cirrhosis.

### DISCUSSION

Although experience with the peritoneal-button operation for ascites is limited, the opportunity to study the reasons for failure in 2 consecutive cases presented itself. In both cases, subcutaneous pockets, which had dense, hyalinized, connective-tissue walls, communicated with the peritoneal cavity. The similarity of the findings in these cases suggests that the formation of such a pocket follows a predictable histologic sequence.

Several factors seem to be of importance in producing this situation. The limitation of the size of the cavity in each case to approximately the limits of the surgical dissection implies that there is a factor of operative trauma with a subsequent attempt at repair. The subcutaneous pocket is maintained by a constant outpouring of fluid from the abdominal cavity. The ascitic fluid alone at times may attain a hydrostatic pressure equivalent to 30 cm of water. In addition, any sudden increase in intra-abdominal pressure is transmitted to this subcutaneous space. Thus, in Case 1 it was suggested that the patient had developed a ventral hernia at the site of operation because of a swelling that appeared in the erect position. This had the configuration of the cavity described and transmitted an impulse on coughing.

Infection in a subcutaneous dead space is often seen in other surgical situations and may increase the extent and degree of scarring. This is suggested in the microscopical section from the cyst wall in Case 1, in which residual foci of mononuclear inflammatory cells were found.

A high concentration of protein in ascitic fluid may, in some cases, be a factor in the formation of a fibrous barrier to absorption of fluid. Foord et al.<sup>3</sup> in a study of ascitic fluid from patients with hepatic cirrhosis, found an average total protein of 1.32 gm per 100 cc, with some as high as 3.09 gm. It cannot be said that the protein concentration was a major factor in the cases presented above, since at no time was the total protein content of ascitic fluid

recorded above 0.68 gm per 100 cc. This value is well within the limits found in edema fluid obtained with Southey tubes from patients in congestive failure.<sup>4</sup> Such a fluid would probably not initiate an active fibrosis.

At some time within the first month after operation the space thus maintained becomes lined with mesothelium but not until the lateral limits of the cavity have become permanently defined by marginal scarring. At this stage the situation approaches that of a bursal cavity, with a smooth gliding surface and an intervening fluid layer. When the abdomen is emptied by paracentesis this space becomes collapsed, but with reaccumulation of fluid it refills much like a "bay" of the peritoneal cavity. Any absorption that occurs from such a space is automatically limited by the small area of surface exposed. In addition, the added storage space provided in the 2 cases (250 and 25 cc respectively) was insignificant.

### SUMMARY

Two cases of hepatic cirrhosis requiring repeated abdominal paracentesis for recurring ascites and treated surgically with a peritoneal button are presented. The effects of these operations were considered negligible after periods of two to four weeks.

An opportunity was provided for post-mortem study of these cases with the discovery of a subcutaneous cystic space having a dense fibrous wall and communicating with the peritoneal cavity in each case.

It is suggested that the formation of a subcutaneous pocket with a dense connective tissue wall and a mesothelial lining follows a predictable histologic sequence. Because of the small area of surface exposed and the fibrous character of the wall, little absorption can take place from such a cavity.

The peritoneal-button operation did not provide an effective, sustained, slow lysis of ascitic fluid in these cases.

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that period varied from 5.3 to 5.7 gm per 100 cc, with albumin-globulin ratios of from 0.3 to 0.5. The hospital course was unrelentingly downhill, with signs of generalized

the costal margin, and the umbilicus was everted. There was a 9-cm, healed, curvilinear incision, with the convexity downward, located 3 cm below and to the left of the umbilicus.

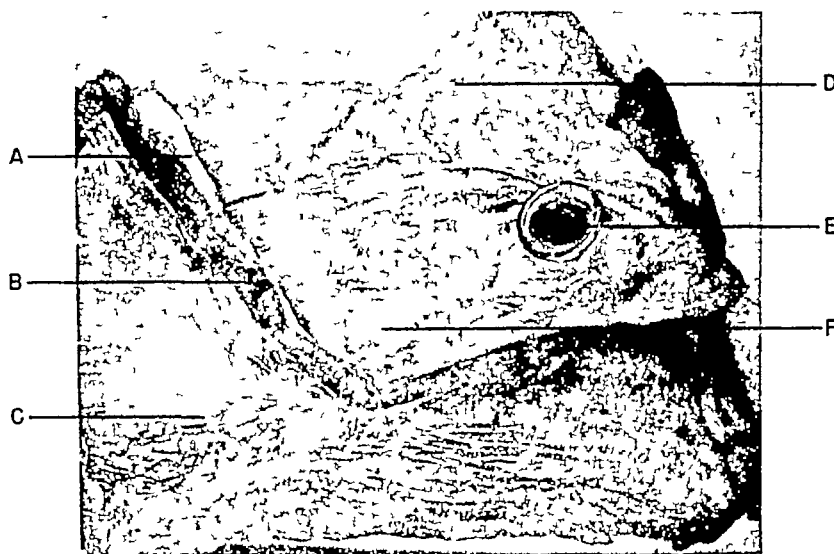


FIGURE 1 Portion of Subcutaneous Space in Case 1

A shows the anterior rectus sheath, B the rectus muscle, C the peritoneum, D subcutaneous tissues, E the superficial aspect of the peritoneal button and F the lining of the cavity.

hepatic insufficiency, cholemia and terminal convulsive episodes.

**Autopsy** Post-mortem examination disclosed marked pitting edema of the legs, genitalia and body to the level of the

Beneath this skin flap was a circumscribed fluctuant area. On incision of this area, a subcutaneous fluid-filled space lined with a smooth, glistening membrane was encountered. The outline of this cavity was irregular, and there was some

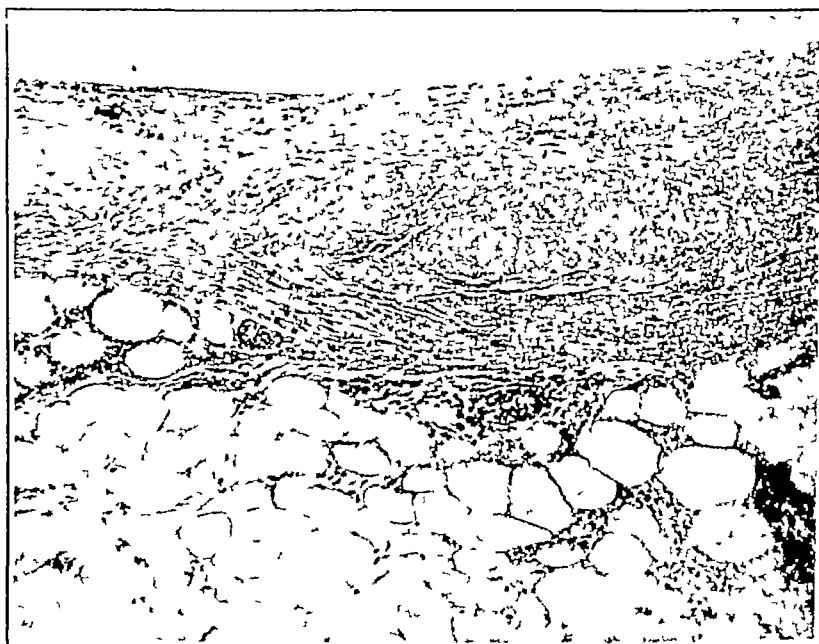


FIGURE 2 Superficial Wall of Cavity in Case 1 ( $\times 100$ )

Note the dense hyalinized connective-tissue layer and the residual inflammatory exudate extending into the adjacent subcutaneous tissues.

costal margins. The skin and sclerae showed a yellowish discoloration, and there were numerous areas of ecchymosis. The superficial veins were prominent over the lower abdomen, upper chest and arms. The abdomen protruded 9 cm above

trabeculation at its margins. The cavity measured 4 by 2.5 by 3 cm. The flanged neck of the superficial portion of the button could be seen occupying the central portion of the floor of the space. When the peritoneal cavity was opened,

*Catheterization of the heart* Forssmann,<sup>10</sup> in 1929, introduced a long, radiopaque catheter first into his own antecubital vein and later into those of patients and succeeded in passing the catheter into the heart without injury. Until recently, this method has been used only occasionally, either for the study of blood pressure and oxygen content in the right side of the heart or for the direct introduction of contrast mediums into the heart. The procedure in the beginning appeared hazardous, and the results did not seem to warrant the chances that the investigator took.

The rapid progress of cardiovascular surgery in recent years, however, and the necessity for all available help in accurate preoperative diagnosis have stimulated further investigation with amazing results. Catheterization is usually performed in centers in which a cardiologist, a cardiovascular surgeon, a physiologist, a chemist and a radiologist work together to solve the puzzles of congenital heart lesions. Results have been published from several of these centers.<sup>11-14</sup>

Sosman<sup>13</sup> and Dexter<sup>14</sup> have given an excellent description of the indications, technic, errors, results, interpretation and value of heart catheterization. A waxed, radiopaque catheter is introduced into the median basilic vein. The catheter has a slightly rigid bend near its end that allows guidance in the desired direction by twisting. Under fluoroscopic control the catheter is passed through the vena cava into the right auricle, into the right ventricle and finally into the pulmonary artery. For other investigative purposes it can be guided through the right auricle into the inferior vena cava. The pressure in these various parts of the heart and large vessels is determined through the catheter, and blood samples are obtained for oxygen-content determinations. Spot films of the catheter are taken in each position in which these determinations are being made. This results in an excellent charting of the conditions within the right side of the heart and the pulmonary artery. Abnormal variations in the pressure of heart chambers and pulmonary artery and of the oxygen content in various locations may be detected and they are often of diagnostic significance, as in interauricular septal defect, in interventricular septal defect, in pulmonary stenosis, and in patent ductus arteriosus. In addition, the abnormal communications within the heart may at times actually be demonstrated by the position of the catheter. The catheter may thus pass directly from the right to the left auricle, from the right into the left ventricle or, in cases of the tetralogy of Fallot, from the right ventricle directly into the overriding aorta. At the time of publication, the authors had performed catheterizations in 100 cases without mishap. Autopsies of patients who later died of causes not connected with the procedure failed to show evidence of damage to the endothelium of the superior vena cava, the right auricle, the

right ventricle, the pulmonary arteries or the valves. It is obvious that this procedure should be performed only when an adequate team is available. In the hands of such a team the information obtained is often invaluable.

*Angiocardiography* In a previous progress report<sup>15</sup> the principle of angiocardiography was discussed. After several attempts by various investigators to demonstrate the heart chambers and the interior of the great vessels by injection of dye into the arm vein either directly or through a catheter Robb and Steinberg<sup>16</sup> demonstrated a practical method in 1939. It consisted of radiography of the heart and great vessels following rapid injection of 30 cc of 70 per cent Diodrast (twice the concentration used in intravenous pyelography). Since the original publication, valuable information has been obtained by this method. The position, size and shape of the heart chambers, valves and great vessels have been studied, and knowledge obtained that had not previously been available. Many questions of topographic anatomy of the living person were clarified. It was possible to obtain a moving film demonstration of the flow of the dye through the vena cava, the right side of the heart, the pulmonary arteries through the lungs to the pulmonary veins, the left side of the heart and the aorta.<sup>17</sup> This was an excellent demonstration of anatomy and physiology of the lesser circulation. The method was used successfully in the differential diagnosis of aortic aneurysms and mediastinal tumors. It was also applied for the study of congenital anomalies of the heart and great vessels. Intracardiac shunts were demonstrated, particularly those from the right side of the heart through a septal defect to the left side and aorta, as in the tetralogy of Fallot and Eisenmenger's syndrome.<sup>18</sup> The patent ductus arteriosus itself was not filled with dye, but accompanying anomalies were visualized,<sup>19</sup> as pointed out below. The method is not a part of the routine examination. It necessitates experience and a special team to produce satisfactory results and should be reserved for research centers.

Recently Chavez, Dorbecker and Celis<sup>20</sup> reported their results with injection of dye through a rather wide catheter, which was introduced in the jugular vein. This article is cited, not because this procedure is expected to be repeated by others (fatalities following the intracardiac injection of dye have been reported) but on account of the illustrations that were made possible by the introduction of dense dye into the heart chambers and the great vessels. They are of special interest in the study of congenital heart lesions.

*Roentgenologic Studies in Specific Congenital Abnormalities*

*Patent ductus arteriosus* In 1939 Gross<sup>1</sup> described the first successful closure of a patent ductus arteriosus. Four years later Donovan, Neuhauser and

Sosman<sup>22</sup> reported from the same hospital the roentgenologic findings in 50 cases that had been verified at operation. This represented at that time a unique experience, since no one had previously had the chance to compare the roentgenologic appearance of the heart and great vessels before and after operation.

The previously vague and contradictory roentgenologic literature on patent ductus arteriosus was now on a solid footing.

The variations from normal found in order of frequency were dilatation of the pulmonary artery, which, although present in 82 per cent of cases, was rarely marked, cardiac enlargement, which was usually only slight and limited to the left side (large hearts were rare in uncomplicated patent ductus arteriosus), dilatation of the left auricle, engorgement of intrapulmonary vessels, which was usually not striking except when combined with endocarditis, exaggerated pulsation of the left ventricle and pulmonary artery, and increased hilar pulsation (so-called "hilar dance"), which was present in a third of the cases.

Postoperatively, the heart size was usually not much changed. Pulsations of the left ventricle and pulmonary artery were found to be decreased, the pulmonary vessels were often smaller than before operation, and the left auricle had decreased in size.

The roentgenologic examination alone does not establish the diagnosis, but it suggests the diagnosis, contributes important confirmatory evidence and bears important witness to the effectiveness of the treatment.<sup>23</sup>

Angiocardiographic studies gave additional information. Steinberg, Grishman and Sussman<sup>19</sup> found localized dilatation of the descending aorta in the region of the patent ductus arteriosus. It was present in 26 of 27 cases. In addition, the main pulmonary artery and its left branch were elevated as if drawn toward the isthmus of the aorta. Dilatation of the main and the major branches of the pulmonary artery was present in 75 per cent of cases. Various degrees of left ventricular dilatation were seen. The ductus itself could not be demonstrated by the opaque medium.

It is rarely necessary to apply angiocardiography to the diagnosis of patent ductus arteriosus. The main importance of studies like these lies in the additional information that is gained for routine roentgenologic examinations. Thus, it should be possible to demonstrate the localized bulge of the aorta during fluoroscopy.

At times, the scar of a closed ductus arteriosus can be seen in adults. A small area of calcification close to the upper edge of the pulmonary artery simulating a calcified lymph node was found to represent calcification in the scar.<sup>24</sup>

*Congenital heart disease with cyanosis.* In 1945 Blalock and Taussig<sup>25</sup> reported the successful surgical intervention in cyanotic patients in whom the pulmonary circulation was impaired, usually owing to pulmonary stenosis and associated defects. The

condition is generally found in the tetralogy of Fallot (pulmonary stenosis, ventricular septal defect, an aorta that rides over the defect and right ventricular hypertrophy). The diagnosis is at times quite difficult, particularly if additional anomalies are present. The roentgenologist can be of help in some cases. The heart, even if not enlarged, shows an abnormal blunting of the elevated apex, the so-called "coeur en sabot" or "sheep's nose heart." The right ventricle is seen to be enlarged, and the pulmonary artery and its branches are small.

Roentgenologic examination is helpful in the differentiation of the tetralogy of Fallot from Eisenmenger's syndrome, a combination of anomalies similar to the tetralogy but without pulmonary stenosis. The clinical picture of the two conditions may be similar, but the Blalock operation is of no help in Eisenmenger's syndrome. Roentgenologically, the pulmonary artery is found to be normal or enlarged in contrast to its narrowing in the tetralogy of Fallot. Angiocardiography at times gives helpful information.<sup>18</sup>

Catheterization of the heart is valuable in the diagnosis of the tetralogy of Fallot. A low pressure in the pulmonary artery and an increased pressure in the right ventricle permit the diagnosis of pulmonary stenosis. At other times, the catheter can be introduced from the right ventricle directly into the overriding aorta and thereby can give a beautiful visual demonstration of the abnormal bloodstream. It is obvious that catheterization of the heart may be of help in the differential diagnosis of the tetralogy of Fallot and Eisenmenger's syndrome.

A great number of variations are possible between the tetralogy and Eisenmenger's syndrome, depending on the degree of collateral circulation for the lung. Bing<sup>26</sup> uses, in addition to catheterization, respiratory studies to determine the pulmonary blood flow. Eisenmenger's syndrome may be called one extreme of these variations with excellent blood flow into the lung through the pulmonary artery. Cases with complete absence or obliteration of the pulmonary artery (so-called "truncus arteriosus solitarius") represent the other extreme. In these cases the lung receives its blood supply from other sources, such as the bronchial arteries. Since the normal hilar shadows are produced by the branches of the pulmonary artery, it is not surprising to find an almost complete absence of the hilar shadow in these cases.<sup>27</sup>

*Vascular ring around trachea and esophagus.* The normal aorta and the large vessels arising from its arch are the end result of a complicated system of six bilateral branchial arteries. This system represents an ideal opportunity for numerous congenital variations, and nature quite often has chosen abnormal variants, the majority of which, although they may represent interesting roentgenologic appearances, do not produce clinical symptoms. The right-sided aorta is the most characteristic example for such a variation. In this anomaly,

the aortic arch lies to the right and posteriorly to the esophagus instead of to the left and anteriorly, as in normal cases. Abnormal displacement of the esophagus and trachea characterizes this condition roentgenologically. Only in rare cases does it produce clinical symptoms such as dysphagia. The recognition of this anomaly is, however, important, since it is not infrequently associated with other congenital anomalies, as in the tetralogy of Fallot.

In certain cases both the right and the left sides of the aortic arch persist, and a vascular ring formed by the two arches surrounds the trachea and the esophagus. Roentgenologically, this anomaly was first diagnosed in 1925.<sup>28</sup> Isolated cases have subsequently been reported. It was found that this arrangement at times produces definite clinical symptoms, particularly of the respiratory tract, including repeated episodes of upper respiratory infection starting in early infancy and stridor, which is more marked during feeding; dysphagia is less striking.<sup>29</sup>

Recent successful ligation and division of one limb of the vascular ring with the resulting freeing of the trachea<sup>30-31</sup> have increased the interest in the roentgenologic appearance of this anomaly, particularly since the diagnosis mainly rests on the roentgenologic findings. Neuhauser<sup>32</sup> describes 4 cases, 2 of which came to operation. The esophagus showed a round pulsating defect posteriorly at the level of the aortic arch. In the anteroposterior view at the same level the esophagus was slightly narrowed from both sides. The trachea just above the carina was seen to be narrowed and displaced anteriorly. The tracheal deformity is best seen after lipiodol installation but may be seen without lipiodol in anteroposterior, oblique or lateral views, if looked for fluoroscopically and with spot films.<sup>31</sup> In some cases the descending aorta lies to the left of the spine, and in others to the right. A correct roentgenologic recognition of this course may be of importance prior to surgical intervention.<sup>31</sup> A vascular ring may easily be missed on routine examination. It is the responsibility of the roentgenologist to think of this possibility, particularly in children with repeated upper respiratory infection and stridor. As stated above, the diagnosis usually depends on his examination. It is likely that some variations in the roentgenologic appearance will be noticed, with an increase in the number of cases observed and operated on.

**Coarctation of aorta.** The roentgenologic changes seen in coarctation of the aorta have been described in many papers. At times, the hypertrophy of the left ventricle, the widening of the ascending aorta, the small aortic knob, the peculiar notching in the upper portion of the descending aorta and, in particular, the erosion of the inferior edges of the ribs produced by the tortuous dilated intercostal arteries are so characteristic as to allow an unequivocal diagnosis. In other cases the roentgenologic findings are less marked. Recent successful resection of the coarcted area has permitted a check of the roent-

genologic findings.<sup>33-34</sup> Gladnikoff<sup>35</sup> analyzed the appearance of the left upper border of the cardiovascular shadows in operated cases. He emphasized the recognition of the dilated left subclavian artery, a medial displacement of the aortic arch and an indentation in the upper portion of the descending aorta as signs of coarctation. When these changes are present in the absence of the common, pathognomonic notched ribs they are of particular diagnostic significance.

**Classification.** The number of congenital anomalies of the cardiovascular system is so large that a simplified grouping has been found to be advantageous. The one generally used is that of congenital heart lesions with or without cyanosis. It is interesting to attempt a classification of these lesions from a completely different approach. Sussman and his co-workers<sup>36</sup> fully recognizing the present impossibility of establishing a complete diagnosis from x-ray study alone, attempt a roentgenologic classification of these lesions. They differentiate lesions with an enlarged pulmonary-artery segment of the cardiac contour, those with a normal or small pulmonary-artery segment and with right or left ventricular enlargement, right aortic arch, and dextrocardia.

Although progress in the diagnosis of these lesions has been so rapid that this classification appears incomplete and somewhat schematic in the light of newer developments, it is quite helpful and is particularly recommended as an introduction to the roentgenologic study of congenital lesions of the cardiovascular system.

A new monograph on the subject of congenital heart disease has been announced by Tausig, and will be available soon. It will represent the experiences of the Johns Hopkins' group, and should prove to be of great interest and value.

#### NEPHROGRAPHY

After the intravenous injection of organic iodine salts like Diodrast for the demonstration of the kidney pelvis and ureters, the shadow of the kidneys increases slightly in density. The increase in density is usually only minimal. Early observers, however, noted that if pyelography was performed while one ureter was acutely obstructed, a fairly marked increase in the density of the kidney might occur on the involved side. If the pain stopped spontaneously, a sudden outpouring of dye into the kidney pelvis and ureter took place, with a decrease in the density and size of the kidney. Wilcox<sup>37</sup> confirmed these clinical observations by experiments in rabbits. Clamping off of one ureter for forty-five minutes resulted in increased size and density of the kidney, but some dye was still excreted into the kidney pelvis. If the ureter was clamped off for sixty minutes, this excretion stopped while the kidney still increased in density. Immediately after release of the clamp the dye poured out into the kidney pelvis, and the kidney returned to its normal size and density. The accumulation of dye in the kidney

parenchyma during the ureteral obstruction was much greater than could be explained by accumulation of dye-containing blood in the kidney. Collection of dye in the uriniferous tubules following the increased pressure in the kidney pelvis was thought to be a decisive if not the entire reason for this phenomenon. More recent discussions on this subject are found in articles by Nowell<sup>38</sup> and by Florence, Howland and Weens<sup>39</sup>.

This phenomenon is of clinical significance. If marked unilateral increase in the density of a kidney and no excretion of intravenous dye on the same side are observed, the presence of acute obstruction can be assumed, although the obstructing agent, such as a small stone or blood coagulum, may not be seen. The phenomenon also proves the presence of a functioning kidney in the absence of dye excretion into the kidney pelvis. In cases of long-standing ureteral obstruction with absent kidney function an increase in density will not take place during the intravenous pyelogram. Finally, the phenomenon proves for all practical purposes that the obstruction is acute.

For a number of years various authors have wondered whether it might not be possible to use this phenomenon for the diagnosis of localized disease in the kidney parenchyma. Recent papers in the literature have attacked this problem and shown some practical results. During intravenous pyelography in a patient with acute ureteral obstruction, Hellmer<sup>40</sup> saw increased density of the involved kidney with the exception of the lower pole, which kept its original density. A repeated intravenous pyelography a few days later, after the colic had subsided, showed excretion into the kidney pelvis. The pelvis was deformed by a tumor of the lower pole. In other words, during the phase of obstruction that apparently had been caused by a blood coagulum, the kidney had increased in density where normally functioning tissue was present but not in the region of the tumor. A similar appearance was produced in a patient who had a renal cyst and acute ureteral obstruction. In a third case of renal colic, an apparently normal kidney pelvis was seen on the involved side, but localized increase in density was noted in the kidney above the pelvis. Three and a half hours after the injection this density disappeared and a second smaller kidney pelvis was filled in the upper pole of the kidney. In other words, this patient had double kidney pelvises and ureters with transient obstruction in one of the ureters. Hellmer called the increased density of the kidney a nephrogram. A satisfactory nephrogram is observed only in the presence of acute ureteral obstruction.

Recently, Weens and Florence<sup>41</sup> published their results with artificial nephrography. These authors introduced a Dourmashkin dilating bougie into the proximal or middle ureter. Then they gently dilated the small rubber bag at the tip of the catheter with 5 cc of mercury. This was followed by intra-

venous injection of 30 to 35 cc of Diodrast (35 percent). If the injection was delayed by ten to twenty-five minutes after the dilatation of the bag only small amounts of dye were seen in the kidney pelvis, and a satisfactory increase in the density of the kidney shadow was obtained thirty minutes after injection of the dye. The kidney was also slightly enlarged. Normal density and size of the kidney reappeared a few minutes after deflation of the rubber bag. Some patients had no pain, others had mild or marked pain, but not enough to prohibit the procedure, if the patient was prepared with 20 mg of Pantopon. Transient hematuria (for not more than one day) was observed in 3 cases, but was probably not more than could be expected from instrumentation. The authors did not report cases in which their method had been of diagnostic value.

Further studies will be necessary to prove that this method is harmless. If so, it will add a new tool to our diagnostic armamentarium useful in individual cases, such as those of unexplained unilateral hematuria with normal routine intravenous and retrograde pyelograms.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 33461

#### PRESENTATION OF CASE

A fifty-five-year-old housewife entered the hospital because of a mediastinal mass.

Eight years previously the patient had been admitted to the hospital for the first time because of a lump in the left breast. There were no other complaints. X-ray studies of the chest, spine and pelvis were negative. A radical mastectomy was performed. The pathological diagnosis was adenocarcinoma (Grade II). The axillary lymph nodes were not involved. A cervical polyp was also removed. This, when examined microscopically, showed extremely severe squamous-cell metaplasia. Sterilization doses of x-ray were administered to the pelvis, and the patient was discharged. Six months later she was readmitted for a hysterectomy. The resected uterus showed an inactive endometrium and chronic endocervicitis. She recovered uneventfully. For several years thereafter she felt perfectly well, and numerous examinations, including at least one chest x-ray film, were entirely negative. Approximately seven years after the original operation the patient reported for a periodic examination complaining of weakness, weight loss and nervousness of six weeks' duration. These symptoms had begun quite abruptly. In spite of a normal appetite she had lost 13 pounds during this period. There had been some intolerance to heat and moderate

palpitation and dyspnea on exertion. She had noticed no swelling in the neck or prominence of the eyes. The bowel habits remained unchanged.

Physical examination at that time revealed a well-nourished woman. The skin was warm and dry. There was a fine, even tremor of the hands and tongue. No abnormality of the eyes was noted. The chest and abdomen were normal. There were no enlarged lymph nodes. The thyroid gland was palpable but not enlarged and gave no bruit or thrill.

The blood pressure was 138 systolic, 80 diastolic, the pulse 100, and the respirations 25.

The basal metabolic rate was +15 per cent. Urinalysis was negative. The cholesterol level was 223 mg per 100 cc, and the cholesterol esters 141 mg. A blood Hinton test was negative.

A routine chest film showed an oval-shaped, soft-tissue mass of smooth outline, measuring 5 or 6 cm in its greatest diameter, in the region of the aortic arch. This mass compressed the trachea and displaced it anteriorly and slightly to the right and also displaced the esophagus somewhat to the right and posteriorly. Fluoroscopy confirmed the finding. The mass did not interfere with swallowing. The esophagus showed no motion in this region, and the mass appeared fixed to both trachea and esophagus. It did not pulsate but could not be separated from the aorta, which it seemed to displace slightly to the left. The heart and lungs were not remarkable. X-ray examination of the bones was negative.

A tracer dose of 100 millicurie units of radioactive iodine was given with 30.8 per cent excretion during the first twenty-four hours and 1.4 per cent during the second. The blood iodine was 8.7 microgm per 100 cc. Repetition of the basal metabolic rate and the blood iodine showed figures of +3 per cent and 5.3 microgm per 100 cc.

The patient was followed closely as an outpatient and improved a great deal during the next few months. The nervousness, palpitation and dyspnea gradually subsided without specific treatment. She gained several pounds in weight, and six months later was admitted to the hospital for study of the



mediastinal mass At that time she felt well, complaining only of slight palpitation on exertion. She had never experienced any difficulty in swallowing or pain in the chest. There had been a slight hacking cough for one or two years but no hemoptysis or increased sputum.

Physical examination revealed no noteworthy abnormality. The thyroid gland was not palpable, but there was slight tenderness to pressure over the right lower pole.

The temperature was 98°F, the pulse 70 to 80, and the respirations 20. The blood pressure was 136 systolic, 90 diastolic.

The x-ray appearance of the mediastinal mass was unchanged. Review of the previous chest x-ray films showed that this same mediastinal shadow had been present five years before and had not changed during this period.

An operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR JOSEPH C AUB A sorely needed mastectomy had been done eight years before entry. The uterine polyp probably never would have become malignant, and why so "much ado about nothing," I do not know. At any rate, x-ray therapy was given, I suppose because of the breast carcinoma. Why the uterus was removed puzzles me. It makes me think that she was a nervous woman or had a nervous doctor, but I get the impression that she was nervous. I do not know whether anyone has ever gone into the psyche of the patient at these exercises.

Seven years later symptoms due to either a neurotic storm or hyperthyroidism developed. That is suggestive of hyperthyroidism, although the basal metabolic rate was only +15 per cent. The mass pushed the trachea forward not backward, and if this report is correct, it was fixed to the trachea, esophagus and aorta. If it was a thyroid tumor it should not have been fixed to the trachea or esophagus and should not have been posterior to the trachea. The description suggests a blood supply from the surrounding area, and therefore implies that the mass was not carried down into the mediastinum like a thoracic goiter.

"A tracer dose of 100 millicurie units of radioactive iodine was given with 30.8 per cent excretion during the first twenty-four hours and 1.4 per cent during the second." That certainly is in favor of hyperthyroidism. A hyperthyroid patient will hold on to a great deal of iodine and not excrete it. The blood iodine was 8.7 microgm per 100 cc. If that was protein-bound iodine, it was above normal values and also suggests hyperthyroidism. Nothing is said about scanning the thyroid gland or mediastinum to see if too much radioactive iodine was retained there.

If the thyroid gland in the neck were shielded — and the amount of radioactive iodine in the medias-

tinum so determined — and if found high one would have to make a diagnosis of mediastinal thyroid tissue. No such therapy as thiouracil was given. Is that right?

DR TRACY B MALLORY Yes.

DR AUB The second basal metabolic rate was +3 per cent, and the second blood iodine was 5.3 microgm per 100 cc. Those are within normal limits, so that we must decide that she did not have hyperthyroid disease. The hacking cough is much more suggestive of neurosis than hyperthyroidism, although patients with mediastinal thyroid glands may cough. The lack of pain in the chest and the lack of sputum and hemoptysis are against a recurrence of the breast tumor.

May we see the x-ray films?

DR STANLEY M WYMAN The original film was initially interpreted as normal. I certainly would call it normal if reading it routinely. As the subsequent examinations unfold, however, and the mass in the mediastinum is noted, it is apparent in review of the first film that there is increased density and that the tracheal shadow does not come down to the upper border of the aorta as it should. This mass is really ovoid. It comes down very close to the aorta and pushes the trachea to the right. In the lateral view the trachea is seen to be displaced anteriorly and is considerably compressed, measuring half the normal diameter. The esophagus is pushed backward. This is a plain film showing the mass. The oblique view shows a good mucosal pattern in the esophagus, with no significant delay or obstruction. The mass is in contact with the wall of the esophagus, and probably adherent to it. The same can be said of the trachea in this view, because the outline of the trachea is slightly irregular and nodular.

DR AUB Is the trachea definitely anterior to the mass?

DR WYMAN Yes, and the esophagus is posterior to it. The statement is made that the mass could not be separated from the aorta, but I believe that one can outline the aortic arch at that point, with the mass lying to its right. The mass apparently has not changed in five years.

DR AUB The first decision to make is whether this mass was benign or malignant. Did it have anything to do with the carcinoma of the breast, or was it related to the uterus? Was this an additional cancer? I do not believe that it was a malignant tumor. It had been present for five years and had not enlarged. It was adherent, which is suggestive of malignancy, but the edges were smooth. It did not grow into the esophagus. There is no evidence that it was growing into the trachea, except for cough, which may have come from impingement on the trachea. Therefore, I think that this was a benign tumor. I shall be disappointed if that diagnosis proves wrong.

The next question is whether this was a benign tumor in contradistinction to intrathoracic thyroid tissue. That seems to me to be the significant differential diagnosis in this case. There are two important points. That the mass was adherent to the esophagus and trachea and did not invade either of them suggests to me that the blood supply was local rather than one carried down from the neck. Therefore, the trouble may have been an inflammatory condition, such as tuberculosis, rather than a benign tumor, but since I do not see any suggestion of tuberculosis in the lung, I have no right to make that diagnosis. The second important factor—and one that I think is also against a mediastinal thyroid gland—is the position of the mass behind the trachea. I do not know of a mediastinal thyroid gland in that position.

There is evidence for hyperthyroidism. As I have already said, the patient appears to have been a nervous woman. Certainly, she was willing to be operated on. There is not a great deal to suggest hyperthyroidism, except for the first radioactive iodine test, and I am not sufficiently convinced about that to lay too much stress on it. At any rate the differential diagnosis rests between hyperthyroidism with a substernal goiter and a benign tumor that had been present a long time. Let us discard the thyroid gland because of the position, adherence and lack of consistent evidence of toxicity. Let us say that it was a benign tumor. If a benign tumor, it must have been one of the connective-tissue tumors, and, on the whole, judging by the law of chances, it would be a neurofibroma. This last part is pure guesswork. I think that the patient should have been operated on if this was an adenoma of the thyroid gland and even if it was a benign tumor, because there was no way of determining what it was, such an operation is good cancer therapy, to avoid the possibility of malignancy and metastasis from the breast, which I do not consider likely. I should guess mediastinal adenoma of the thyroid, and I believe that that diagnosis is wrong. What was the hospital preoperative diagnosis?

DR HELEN B PITTMAN: We went through all the same troubles that Dr Aub has, but for a much longer time. The patient was not a nervous woman. She was co-operative and somewhat irritated that we paid so much attention to the symptoms that did not bother her. Hysterectomy was done because she had an easily bleeding cervix that looked abnormal, and we thought that it should be removed. We followed her in the thoracic clinic, and Dr Schatzki did a great deal of fluoroscopy on her. The initial group that saw her thought that the diagnosis fell between metastatic node and mediastinal thyroid gland, and since one does not operate on metastatic lymph nodes in the mediastinum, she was given iodine, to determine if we could pin the trouble on the thyroid gland.

She remained in good health, and the mass did not change in appearance. It was decided that it was benign.

Some months later the opinion was that the lesion was probably either a bronchiogenic cyst or an intramural or extramural tumor of the esophagus, which ought to be removed as good general prophylaxis.

DR EARLE M CHAPMAN: This patient was seen in the Tumor Clinic, where opinion varied. I can sum it all up by reading the final note made by Dr Cope: "The diagnosis is impossible, short of operative exposure."

DR DONALD S KING: Dr Castleman thinks that I ought to be able to name this lesion, but I cannot. I did not see the patient. It seems to me more like a tumor in the esophageal wall. That is the best that I can make of it.

DR WYMAN: I would be surprised if this were a tumor in the esophageal wall, Dr King.

DR KING: Could it not be in the wall and not involve the mucous membranes?

DR WYMAN: Such tumors usually cause more spreading of the esophagus, especially a mass of this size. With intramural lesions the esophagus appears more adherent, is displaced more and is thinned.

DR KING: Yes, but I remember a case that did not, I therefore think that it is still possible that this was an esophageal-wall tumor.

#### CLINICAL DIAGNOSIS

Mediastinal cyst

DR AUB'S DIAGNOSIS

Benign intrathoracic tumor of connective tissue  
(not intrathoracic goiter)  
Neurofibroma?

#### ANATOMICAL DIAGNOSIS

*Bronchiogenic cyst*

#### PATHOLOGICAL DISCUSSION

DR MALLORY: This patient was operated on by Dr Richard H Sweet. He found a tumor mass very densely adherent to the trachea, to the esophagus and to nearly all the other surrounding structures. In attempting to mobilize it he broke the wall and released some mucoid fluid similar to that commonly seen in bronchiogenic cyst. He was eventually able to free the cyst entirely and get it out in a collapsed state.

The microscopical sections from the wall of the cyst showed that it was lined with ciliated respiratory epithelium. Usually, cartilage is also to be found in the cyst wall. In the case under discussion we did not succeed in identifying cartilage, although there were old foci of calcification. This is not a rare location for bronchiogenic cysts. It is the same region in which tracheoesophageal fistulas

are found, and abnormal bronchial buds in this area are common and may develop into cysts of considerable size

DR AUB I do not believe that one can make that diagnosis before operation, do you?

DR MALLORY It would be no more than a guess

## CASE 33462

### PRESENTATION OF CASE

A thirty-five-year-old para II was admitted to the hospital because of abdominal pain

The patient's menstrual periods had begun about fourteen years before admission, occurring every twenty-eight days and lasting three to five days with no excessive bleeding until about seven years later, when she became pregnant. The pregnancy ended in a miscarriage, after considerable bleeding requiring a dilatation and curettage. She had two subsequent pregnancies six and three years before entry. With the last pregnancy she spent five months in bed to prevent a miscarriage and after delivery had excessive periods. Eight months prior to admission she had a dilatation and curettage and fifteen hours of radium treatment. Following this she developed a "pelvic abscess," which required five weeks of bed rest, penicillin and general supportive care and was finally drained rectally. Subsequent to the radium treatment the patient developed hot flashes, and the periods ceased. Injections prevented the hot flashes. After this the patient did well until four months before entry, when she began having pain almost constantly in both lower quadrants in the suprapubic region. The pain was sometimes relieved by urination or bowel movements. It was not referred, and had no association with food intake. Twelve hours prior to admission the patient had nausea and vomited once. She had been passing gas and had been anorexic for forty-eight hours prior to admission. She denied chills, fever or vaginal discharge and stated that she had recently lost about 12 pounds of weight.

Physical examination disclosed no enlargement of the heart, and the lungs were clear. In the right lower quadrant of the abdomen there was a hard tender mass about the size of an orange. Over this was a small olive-sized mass that rolled under the palpating finger and produced pain. A pelvic examination was not done.

The blood pressure was 130 systolic, 80 diastolic. Examination of the blood revealed a hemoglobin of 10 gm and a white-cell count of 10,000. The

of the abdomen revealed small in both the large and the small intestine, and a poorly defined area of indistinctness in the right pelvis. There were spots of calcification. The temperature,

pulse and respirations remained normal, and on the second hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR JOE V MEIGS This patient must have had some endocrine disturbance or an anatomic abnormality in the genital tract, such as a fibroid, to account for the multiple miscarriages. Following her last pregnancy she had abnormal menses and eight months before admission was treated with radium. It is impossible to guess the amount of radiation she received merely from the duration of the treatment, but it was obviously great enough to induce menopausal symptoms. I believe that it is not wise to use radium in a woman only thirty-five years old with a benign condition. At that age the patient would be far better off if operated on. The uterus, cervix and if necessary the tubes could be removed, but the ovaries should be left in place. Then the patient would not be condemned to the prolonged use of estrogens to combat menopausal symptoms. This patient was evidently treated with estrogens, since the symptoms were relieved by "injections." Again, we do not know the dosage or the duration of the parenteral treatment. It would be important to know if the treatment was continued up to the time of admission.

DR TRACY B MALLORY We have no further information about that.

DR MEIGS That radium therapy is not without danger and may produce serious consequences is demonstrated by this case, since a pelvic abscess developed after its use. This abscess may have been due to perforation of the uterus at the time of application of the radium, or it is possible that a pre-existing pelvic inflammatory disease flared up following the treatment. Certainly, the patient developed salpingitis with a pelvic peritonitis, which was drained through the rectum.

One can imagine that the most recent episode, which brought the patient to the hospital, represented another flare-up of the process. Again, she may have had enlargement of the uterus that was due to the accumulation of fluid above a cicatrix of the cervix. The estrogens, if continued, may have induced bleeding from the endometrium, and the blood could not escape through the cicatrized cervix, producing a hematometrium. That would cause pain.

The occasional relief of pain when the patient urinated or moved the bowels suggests inflammatory disease. However, she denied chills, fever or vaginal discharge. The white-cell count was normal, and the hemoglobin satisfactory. She had complained of anorexia and had recently lost 12 pounds in weight, but there was little evidence of any systemic reaction such as one would expect with inflammation.

I find it difficult to understand why no pelvic examination was done. It might have helped explain the confusing findings on abdominal palpation. The

mass described in the "right lower quadrant" could, I suppose, be an enlarged uterus full of blood, and the small tender mass a fibroid. Or the big mass itself could have been a fibroid, with a smaller one attached to it. The mass could equally well have been an ovary—either an ovarian abscess or simply a large cyst of the ovary. The x-ray examination does not help me. X-ray diagnosis can be incorrect in interpreting masses in the pelvis.

I believe that the best bet is that this young woman, who had a radiation-induced menopause, developed pelvic inflammation, was treated with estrogen for the hot flashes and then developed enlargement of the uterus without vaginal discharge, must have had a cicatrix of the cervix, with an accumulation of blood in the uterine cavity.

My diagnosis is radiation cicatrization of the cervix and hematometrium. My second choice is some sort of inflammatory mass associated with the right adnexa, representing a recurrence of the pelvic inflammatory disease.

#### CLINICAL DIAGNOSIS

Pelvic inflammatory disease?

#### DR MEIGS'S DIAGNOSES

Cicatrix of cervix, post-radiation, with stenosis of cervical canal  
Hematometrium

#### ANATOMICAL DIAGNOSES

*Cicatrix of cervix, post-radiation, with stenosis of cervical canal*  
Hematometrium  
Leiomyoma of uterus

#### PATHOLOGICAL DISCUSSION

DR MALLORY: Dr Meigs's prediction was correct. At operation an extensive pelvic peritonitis was found with dense adhesions binding all structures together, but no pockets of pus or evidence of acute inflammatory reaction. The uterus was large and soft, and there was a small fibroid on its surface. A hysterectomy was performed with some difficulty. When the uterus was opened the cervical canal was found to be completely obliterated, and the uterine cavity was full of blood, of which part was fresh and part obviously old.

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## THE DIETARY TREATMENT OF HYPERTENSION

THERE has been of late a considerable renewal of interest in the dietary treatment of essential hypertension. Doubtless from time immemorial and certainly from recorded medical history, much attention has been paid to diet in health and disease. A good deal of the benefit from diets has been found incidentally or empirically.

In 1866 Karell<sup>1</sup> introduced a diet for the effective treatment of edema and heart failure. It was a starvation ration consisting of only 800 cc of milk a day, and was limited in salt intake and fluids, as well as in calories. This diet is still, on occasion, used in the initial treatment of severe congestive heart failure.

In the early years of the twentieth century it was clearly proved that a low-sodium intake could clear edema due to congestive heart failure.<sup>2</sup> Hypertension was not specifically described in these cases, however, and it is doubtful if the blood pressures were recorded. When hypertension became well recognized as a cause of disease, dietary treatment of various sorts was instituted. The commonest of all kinds of such diet has been a simple reduction diet, low in calories, mostly because of restriction of fat and carbohydrates. Not infrequently there has also been, with a reduction of weight, a reduction of blood pressure, although such a relation has not always been found.

Moreover, during the early part of this century and even earlier, it had been customary to reduce the protein intake, largely by restriction of meat and eggs in patients with so-called "Bright's disease" with or without actual nephritis or congestive heart failure that might be secondary to hypertension. With a restriction of the amount of any food taken, but particularly with restriction of meat and eggs, the salt intake was coincidentally reduced and may well have had an important bearing on some of the good results noted, especially in patients with congestion.

In the 1920's, considerable interest was evoked in the use of a low intake of sodium chloride in the treatment of hypertension, with emphasis on the chloride. During those years there were controversies about the effects<sup>3, 4</sup> but the reduction of sodium itself was apparently not so great at that time as recently.

A few years ago, Dr. Kempner, of Duke University, instituted the so-called "rice diet" (2000 calories, 20 gm of protein, 460 gm of carbohydrates, 5 gm of fat, 0.2 gm of sodium and 0.15 gm of chloride) in cases of nephritis and renal insufficiency. In the course of this study it was observed that the previously high blood pressure not infrequently fell to or toward normal figures. This led to the institution, three or four years ago, of the same diet for the treatment of hypertension per se. The success in some cases in relieving symptoms, in lowering the blood pressure and in the decrease or actual clearing up of evidence of serious hypertensive effects on heart and eyegrounds led to its adoption by Kemp-

ner<sup>4</sup> 'more or less routinely in the treatment of hypertension. Slowly, knowledge of this therapy has spread from Durham, and the rice diet is being tried in other places, but with no extensive knowledge yet regarding the percentage of favorable results or the persistence of such favorable results over a prolonged period in the course of follow-up study. The percentage of favorable results in a series of 500 patients has just been calculated for a "seminar" to appear in the *American Journal of Medicine*. A lowering of the blood pressure was found in 181 (66 per cent) of the 271 patients with hypertensive vascular disease without evidence of renal excretory dysfunction (1 of the 90 so-called "negative patients" died), and in 129 (56 per cent) of the 229 patients with hypertensive vascular disease with renal involvement (25 of the 100 "negative patients" died after an average period of thirty-nine days).

The rice diet, based on rice itself largely because of its economy, availability and easily assimilated protein, also contains fruits and sugar, but no vegetables, meat, milk or salt. The first course of treatment consists of a strict diet, usually for four to twelve weeks, after which there is the addition of a potato or two a week and a small amount of meat. Very slowly, the diet is liberalized with the substitution of one third of vegetables for one third of the fruit and, finally, with the addition of more meat, but a full routine diet is not, as a rule, resumed. If symptoms recur or if the blood pressure rises, the original diet is started again. No adequate comparison has been made between the effects of the rice diet and those of Smithwick's lumbodorsal sympathectomy, which has proved its success in a certain percentage of hypertensive patients. Both therapeutic measures are radical and, it is hoped, may be replaced some day by simpler therapy.

Some investigators have believed that the benefit of the rice diet may be ascribed to its low sodium content, but as yet this theory has not been proved. The renewed interest in the therapy of hypertension by low-salt intake in the last few years has stimulated such dietary treatment in a number of different centers in the United States and Canada. It is still too early to determine what the ultimate results may be. Various degrees of sodium restriction are in-

volved, and various types of diets, with or without additional therapy, are being tried.

It should be possible after careful studies during the next two or three years to learn what diet or diets may be useful in hypertension and how they work — whether by restriction of sodium, protein and fat, including cholesterol,<sup>7</sup> by combination of such restrictions or for other reasons. It is necessary by detailed studies and by careful follow-up to work out careful answers to the questions that have been propounded.

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#### MADAME PRESIDENT

Boston claims with pride the distinction of being the birthplace and family home of the first woman president of the American Public Health Association, Dr. Martha May Eliot, who assumed that office on October 9, 1947.

Dr. Eliot is a member of a family that has consistently made its contribution to the public welfare. Her grandfather, William Greenleaf Eliot, founded Washington University in St. Louis, her father, Dr. Christopher R. Eliot was a clergyman of Dorchester. Her brother, the Reverend Dr. Frederick May Eliot of Cambridge is president of the American Unitarian Association, her sister, Dr. Abigail Adams Eliot is director of the Nursery Training School of Boston. The late Charles W. Eliot, former president of Harvard University, was a second cousin of the Reverend Dr. Christopher R. Eliot. Charles W. Eliot's son, the Reverend Dr. Samuel Eliot, preceded Dr. Frederick M. Eliot as president of the American Unitarian Association. Certainly public service has become a heritage and a tradition in the Eliot family!

Dr. Eliot was born in Dorchester on April 7, 1891. She attended the Winsor School and Radcliffe College, from which she graduated in 1913. During the

year after leaving college she worked in the Social Service Department of the Massachusetts General Hospital, in the Children's Cardiac Clinic. In 1918 she received her degree in medicine from Johns Hopkins University School of Medicine after which she interned at the Peter Bent Brigham Hospital.

She became in 1921 the first woman resident physician at the New Haven Hospital, with a teaching position at Yale University School of Medicine. In these early years she made a noteworthy study on rickets for the United States Children's Bureau, and she shortly became a member of the bureau's staff. In 1934 she became assistant chief of the bureau, and in 1941 associate chief. In that year she was sent by the United States Government on a military mission to England to study the impact of war on children under conditions of bombing and evacuation. During the summer of 1947 she was on the staff of the International Children's Emergency Fund Committee of the United Nations, in which capacity she made two trips to eastern Europe, penetrating even the "iron curtain" in the interest of the children of those countries. She is particularly well known as the author of the Emergency Maternal and Infant Care program.

Dr. Eliot has stood firmly for governmental support of health services for all the people—one of the controversial subjects of the day. Whichever side of the argument her professional colleagues may favor, they must respect her opinions and honor her achievements. She has earned her positions on the health councils of the land.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REPATRIATION OF WORLD WAR II DECEASED

The Department of Public Health has informed local boards of health regarding the plans and regulations of shipment of World War II deceased.

Upon arrival of the remains in the local community where they are to be buried, the next of kin will arrange with the proper authorities for the issuance of the burial permit. The local board of health of the community wherein burial is to be made will issue a burial permit covering the remains of the World War II dead to any licensed funeral director in the state upon presentation of the decedent's name, rank and serial number, which is stenciled on the end of the outside shipping case, and the basic health permit number as indicated on the basic health permit marker, which is attached

to the end of the shipping case. No Massachusetts Standard Certificate of Death Form R-301 need be filed except for persons who died in the service abroad since the end of hostilities. In such cases a complete death certificate will be returned with the transit permit.

In filling out the burial permit, the phrase "World War II Deceased" will be entered under the cause of death.

Additional routine information as required should be requested of the funeral director, such as residence of next of kin and plan of interment.

The following rule was adopted by the Board of Registration in Embalming and Funeral Directing at its meeting held on September 26, 1947:

Rule 46-A—No casket, box or other container in which a body that has been disinterred and shipped to this country from foreign soil, shall be opened before burial of such body in the Commonwealth.

The outside shipping case is not included in the above rule.

## CANCER INSTITUTE

A cancer institute will be held in Boston from November 16 to 21, inclusive, under the joint sponsorship of the Massachusetts Department of Public Health, Harvard School of Public Health, American Cancer Society (Massachusetts Division, Incorporated), Massachusetts Medical Society (Committee on Cancer), Massachusetts Dental Society and Boston Health League.

A public meeting, sponsored by the Harvard School of Public Health, will be held in the amphitheater of Building E, Harvard Medical School, at 3:30 p.m. on Sunday, November 16. A conference for state-aided cancer-clinic workers and a meeting for medical social workers, nurses and similar personnel will be held at the Red Cross Chapter House, 17 Gloucester Street, from 10:30 a.m. to 4:00 p.m. on Monday, November 17. A clinic for members of the Massachusetts Dental Society will be conducted at the Palmer Memorial Hospital, 195 Pilgrim Road, at 2:00 p.m., with a luncheon meeting of cancer-control committees at Vanderbilt Hall, Harvard Medical School, at 1:30 p.m. on Tuesday, November 18. On Wednesday, November 19, from 10:00 a.m. to 4:30 p.m., a meeting for state-aided cancer-clinic staffs will be held in Amphitheater 3A of the White Building, Massachusetts General Hospital. The American Cancer Society (Massachusetts Division, Incorporated) will present a radio program on Thursday, November 20. A meeting of medical social workers, nurses and similar personnel will be held in the auditorium at 100 Nashua Street from 10:15 a.m. to 4:00 p.m. on Friday, November 21.

## ROBERT N. NYE MEMORIAL FUND

The American Cancer Society, Incorporated (Massachusetts Division), announces that the Robert N. Nye Memorial Fund is in excess of \$2245.

## ROBERT NASON NYE

(1892-1947)

Robert Nason Nye was born in Springfield, Massachusetts, on June 3, 1892, the son of George Nye, Jr., and Mabel Francis (Nason) Nye. Entering Harvard College in the fall of 1910 he qualified for his degree *cum laude* in 1913. He spent the following year at the Harvard Medical School and then went into business. He returned a year later, received his degree *cum laude* in February, 1918,

and enrolled in the Medical Reserve Corps, although he was never called to active duty, after a few months in the Pathology Laboratory of the Boston City Hospital, he served a medical internship at the Massachusetts General Hospital. He subsequently worked for a year in the Medical Research Laboratory of the Hospital, returning in 1920 to the Boston City Hospital as assistant pathologist. In 1922 he was appointed assistant director of the Antitoxin and Vaccine Laboratory of the Massachusetts Department of Public Health, resigning to become assistant physician to the new Thorndike Memorial

Laboratory at the Boston City Hospital. He became associate physician to the Laboratory in 1929. He had been assistant professor of bacteriology and immunology at the Harvard Medical School since 1942.

Meanwhile, in 1937, he had turned his talents in a new direction, succeeding the late Dr. Walter P. Bowers as managing editor of the *New England Journal of Medicine*. The capable leadership that he brought to the *Journal* has been largely responsible for its continued progress and the maintenance of its high standards.

He became a member of the Committee on Information, Division of Medical Sciences of the National Research Council in 1940, and during the war was a member of the Committee on Information of the Procurement and Assignment Service of the War Manpower Commission.

Dr. Nye was an editor of *War Medicine*, recently published by the American Medical Association,

a councilor of the Massachusetts Medical Society, a trustee and treasurer of the Boston Medical Library, a councilor of the Harvard Medical Alumni Association and director at large of the Massachusetts Tuberculosis Association. He was a member of the American Society for Clinical Investigation, the American Association of Pathologists and Bacteriologists, the American Association of Immunologists, the American Academy for the Advancement of Science and the Society of Experimental Biology and Medicine.

In 1917 he married Katherine Blake Lincoln, of Springfield, who survives him with their two children, Mrs. William Caldwell Coleman, Jr., of Baltimore, and George Nye, and two grandchildren, William Caldwell Coleman, III, and Robert Nason Nye, II.

Here are his achievements and his record — the record of one who did well that to which he set himself. In work or in play he did not put his hand to a task or his mind to a problem without mastering

it. Whether in keeping bees or in luring a salmon or in turning from the exacting science of bacteriology to the exacting duty of editing and managing a leading journal of medicine, he did the thing in hand superlatively well.

We shall remember him for his varied contributions to the changing pattern of medical science and literature and sociology. We shall remember him with deeper feeling as an ardent lover of life with a peculiar sensitiveness to the muted strings of nature — among his garden flowers or looking for the first hepatica bloom on his wooded island, or stopping on the trail to identify a warbler that had dallied in its northern flight or casting a fly over a ripple on the lake he loved so well. The goal of life was in the living of it.

Knowing that Nature never did betray  
The heart that loved her; 'tis her privilege  
Through all the years of this our life to lead  
From joy to joy





## MISCELLANY

### PRIZE SUBSCRIPTION

The prize subscription offered by the *New England Journal of Medicine* for the best undergraduate contribution to the *Tufts Medical Journal* has been awarded to William H. Waugh for his paper "The Sites and Mechanism of Plasma Globulin Formation," which appeared in the June, 1947, issue. The paper "Some Achievements of the Public Health Laboratory," by Miriam Manning received honorable mention, it appeared in the December, 1946, issue. According to custom, these students will be given a two-year and a one-year subscription to the *Journal*, respectively.

### NOTES

Dr Robert E. Gross, surgeon-in-chief of the Children's Hospital, Boston, and William E. Ladd Professor of Child Surgery, Harvard Medical School, was awarded the Matas Medal at New Orleans on October 3, 1947.

In 1933, under the will of Violet Hart, a fund was established for the purpose of awarding a medal from time to time to a surgeon who had contributed to the advance of surgery of the blood vessels. It is named in honor of Dr. Rudolph Matas, of New Orleans, a pioneer surgeon in this field. Since 1933 there have been four awards to Dr. Mont Reid, of Cincinnati, Dr. DeSantos, of Portugal, Dr. Daniel Elkin, of Atlanta, and, in 1947, to Dr. Gross.

The medical profession of Boston takes pride in this tangible recognition of the abilities of one of its fellow members.

Dr. Kendall Emerson, managing director of the National Tuberculosis Association since 1928, has announced his resignation, effective January 1, 1948. He will be succeeded by Dr. James E. Perkins, deputy commissioner, Department of Health, State of New York.

## BOOK REVIEWS

*Anesthesia in General Practice*. By Stuart C. Cullen, M.D. 8°, cloth, 260 pp., with 36 illustrations and 4 tables. Chicago: The Year Book Publishers, Inc., 1946. \$3.50.

This book represents a necessary step in the development of literature on anesthesiology. It is a good textbook for students, and as such fills a pressing need. The discussion of anesthetic agents, methods of administration, drugs, preoperative medication and postoperative care of the patient is not exhaustive but is clearly and concisely outlined. The chapters on shock, oxygen therapy and explosion hazards are treated in their proper relation to the practice of anesthesiology. The cartoons presented seem somewhat juvenile at first glance. Actually, they are effective in focusing the attention of the student on important principles of diagnosis and treatment of drug reaction and oxygen lack. This book is a straightforward presentation of basic facts in the practice of anesthesiology.

*Personality of the Preschool Child. The child's search for his self*. By Werner Wolff, 8°, cloth, 341 pp., with 118 illustrations. New York: Grune and Stratton, 1946. \$5.00.

This excellent book is based on the idea that, although detailed studies of the child's overt behavior are available, an attempt should be made to study "the hidden forces and motivations" of such behavior. The task was to design experiments to explore the spontaneous verbal, graphic and dramatic expressions of children and thus to gain a unifying concept. The approach is called "experimental depth psychology." The author thinks that the young child's action can be interpreted as a continuous search for his self. It is a fundamental fact that the child's world is different from that of the adult and that the child cannot be understood in any terms taken from adult psychology. The young child lacks all the experience of an adult, who fills in continuously the gaps in his own experience by pieces of knowledge that he has acquired from his surroundings. The preschool child, with little or no knowledge and facing constantly new experiences, has not yet an understanding of the value of the

various items he encounters. The child is therefore forced to overbridge the gaps by imaginary interpretations drawn from fantasy rather than from experience.

The book is divided into three parts. The first discusses several aspects of the child's mind, conditions and social activities and his concept of reality. The second attempts a construction of the child's personality through the reflection of his various activities and reactions. In this section, play and drawings are freely used for the exploration of the preschool child's world. The only criticism that could be attached to this otherwise interesting study is that the author relies in his interpretations too much on the expressions of the child himself or on his own interpretation of what he thinks the child meant. The third section discusses the principle of children's art, as well as the child and the adult and methods in child psychology.

By virtue of the fact that the author emphasizes in the beginning the differences between the adult's and the child's world, some of the interpretations appear not too convincing, and the author draws too heavily on other sources of experience like psychoanalysis to achieve the goal of a unifying interpretation of the child's personality—a knowledge that the author's own material cannot provide in every direction.

The book, although written primarily for psychologists and not psychiatrists, contains a great wealth of material, and will prove of benefit to any pediatrician or psychiatrist.

*The Principles and Practice of Medicine*. Originally written by William Osler, M.D., F.R.C.P. Designed for the use of practitioners and students of medicine. By Henry A. Christian, M.D., LL.D., (Hon.) Sc.D., Hon. F.R.C.P. (Can.). Sixteenth edition. 8° cloth, 1539 pp. New York: D. Appleton-Century Company, Inc. 1947. \$10.00.

Dr. Osler published his monumental textbook in 1892 and was solely responsible for the first seven editions. In 1916 Dr. Thomas McCrae became a joint author, and in 1919 after Dr. Osler's death he carried the work through the twelfth edition, published in 1935. Dr. Christian assumed the authorship with the thirteenth edition in 1938 and has continued to revise the succeeding editions. He inaugurated an innovation by appending lists of selected references to each subject and thus enabling the reader to follow up any given subject. These references include the literature of 1945.

The new edition has been thoroughly revised to bring it up to date, resulting in the complete resetting of more than nine hundred pages.

The book has had a remarkable publishing history. At least eighty-four separate printings have been issued simultaneously in America and England through the fifteenth edition. In recent years the publishers have indicated the printings by a numeral found at the end of the index. Unfortunately, in the sixteenth edition the system has reverted to number one, indicating the first printing of this edition. The binding has been varied. The first four editions were issued in four styles, two in leather and two in full cloth, and in four different colors. Editions five to seven were bound in brown half leather and full red cloth. With the thirteenth printing of the eighth edition the binding was standardized in one style of full red cloth that has been continued to date. The first printing of the first edition is identified by the date of the advertising pages, the misprinting of "Gorgias" as "Georgias" in the quotation from Plato and the lettering on the backstrip (the edition number was not printed on the backstrip of editions one to seven). The first English printing appeared both with and without the Plato error. The fourth English edition was pirated, resulting in two issues by Pentland and by Kimpton. The work has been translated into three Chinese editions, as well as into French, German, Spanish and, in 1945, Portuguese.

The Boston Medical Library has a unique collection of editions of this textbook, originally begun by Dr. Henry R. Viets and continued by the Library. It numbers to date one hundred different printings in the various bindings of the American edition, as well as the English editions, all the translations and the first American and English printings. Dr. James C. Carr has prefixed to the sixteenth edition a short history of medicine (1892-1947) as told in the sixteen editions.

The popularity of the book is attested by its numerous printings over a period of fifty-five years and the fact that the

publishers are making an initial printing of this 1947 edition larger than that of any of their popular texts for the last twenty five years. The material is well organized and emphasizes symptomatology, diagnosis and treatment. The printing is well done with a good type on light paper resulting in a comparatively light volume for the number of pages. A remarkable comprehensive index of 147 pages concludes the book. It is hoped that with the seventeenth edition wider margins will be restored to the pages.

The book is an ideal reference text for the busy practitioner and should be in all medical libraries.

*The Ranks of Death. A medical history of the conquest of America.* By P. M. Ashburn, M.D. Edited by Frank D. Ashburn. 8", cloth, 298 pp. New York: Coward-McCann, Inc., 1947. \$5.00.

The manuscript of this posthumous volume, by the well known author of *The Elements of Military Hygiene* and *A History of the Medical Department of the United States Army*, was found among his papers and prepared for publication with an appropriate preface by his son. It presents a medical history of the conquest of America particularly the part played on both sides by disease including famine, scurvy, smallpox, typhus, measles, malaria, yellow fever, tuberculosis, pneumonia, diphtheria, dysentery, typhoid fever and syphilis. In general these auxiliaries inflicted more casualties on the aborigines than on the invaders whose resistance and intelligence were superior. In his epilogue, the author suggests that the race can best keep well by acquiring immunity.

This is an exceedingly valuable volume, not only in itself but also as a source for future students and writers. A large amount of technical material allied with the text is collected in three appendices where it is easily available for reference.

*Studies and Essays in the History of Science and Learning Offered in Homage to George Sarton on the Occasion of his Sixtieth Birthday 31 August 1944.* Edited by M. F. Ashley Montagu. Ph.D. 8", cloth 596 pp. with illustrations and portrait. New York: Henry Schuman 1947. \$12.00.

George Sarton, the distinguished professor of the History of Science at Harvard University and author of an indispensable tool for workers in the field of science and medicine, his *Introduction to the History of Science* attained his sixtieth birthday on August 31, 1944. The present volume, whose publication was much delayed by the war, was presented to him by his friends in manuscript form on that occasion. The contents reflect the wide basis on which the history of science rests, for among the twenty seven essays written in homage to Sarton the following topics are given considerable treatment: Vesalius on bloodletting; da Vinci as a military engineer; the link between heredity, positivism, ethiogenesis; Galileo's Platonism; transfinite numbers; Babylonian astronomy; Chinese grammar maps of the Missouri River; and public bureaucracy and a biography of George Green the physicist. The interest of everyone with scientific curiosity should be stirred by one or more of the scholarly and informative papers in this exceptionally pleasing volume. Not the least important is the all too brief biographical sketch of the modest master of the subject, which lets in a little more light on his complex career transplanted in April 1915 from a war torn Belgium to what at first was a cold and unappreciative America. Slowly his outstanding rank in history and science was appreciated, and in 1940 among many other honors, Harvard made him a full professor.

The volume is well edited and well printed. An excellent portrait of Sarton serves as a frontispiece. The publisher has shown great taste in the format. The only drawback is the price, made necessary by the times and in spite of "benefactors" which may well serve to keep the book out of deserving hands.

*The Self You Have to Live With.* By Winifred Rhoades. Revised edition. 8", cloth, 254 pp. Philadelphia: J. B. Lippincott Co., 1947. \$2.00.

The author of this book assisted Dr. Joseph H. Pratt in building up the Thought Control Clinic of the Boston Dispensary. For years he has worked with patients referred to that clinic by doctors in various parts of New England

during which time he has witnessed and helped the development of group psychotherapy in a unique way.

This book is one of the fundamental chapters from his experience. It contains common-sense points of view and ideas that he has used in dealing with patients who have expressed a wish to help themselves by psychologic means. It is not so much a profound as it is a practical book. The ideas are an interesting rephrasing of old truths in a form that is handy for clinical use, rather than new discoveries. The volume belongs with books that are valuable as a form of self help and as such can be considered a contribution to bibliotherapy.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Office Immunology including Allergy. A guide for the practitioner.* Edited by Marion B. Sulzberger M.D., professor of clinical dermatology and syphilology and director New York Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital and Rudolf L. Baer M.D., instructor in dermatology and syphilology, New York Skin and Cancer Unit New York Post-Graduate Medical School and Hospital. 8" cloth 420 pp. Chicago: Year Book Publishers, Incorporated 1947. \$6.50.

This volume, the joint work of six physicians, is published as one of the *General Practice Manuals*. It is principally concerned with the infectious diseases and dermatologic and other allergies. Emphasis is placed on diagnosis, treatment and preventive inoculation. Drug eruption, eczematous contact type allergic dermatitis and patch testing are fully discussed. The manual is written for the practicing physician and endeavors to assemble in one volume the essential material now scattered through many volumes.

*Medical Aspects of Growing Old.* By A. T. Todd M.B. (Edin.), M.R.C.P. (Lond.) honorary physician, Bristol Royal Infirmary. 8" cloth 164 pp. with 15 illustrations. Bristol: John Wright and Sons Ltd. 1946.

This manual, which has been written for the laity as well as for physicians, has been kept as simple as possible. The first part treats of mentality, physiology of the digestive tract and diet, retirement and the use of leisure time, exercise and sleep. These chapters are followed by a discussion of conditions met with in the aged: constipation, cardiovascular disturbances, blood pressure, emphysema and genitourinary troubles in both men and women. There are also chapters on the care of the nose, skin, hair and feet. The material is well organized and well written. The publishing is excellent. The advice given is sensible and the manual should prove valuable to those interested in the medical care of the aged.

*Year Book of Endocrinology, Metabolism and Nutrition for 1946.* Endocrinology edited by Willard O. Thompson, M.D., clinical professor of medicine, University of Illinois College of Medicine, attending physician (Senior Staff) Hennrich Hospital and attending physician Grant Hospital of Chicago. Metabolism and Nutrition edited by Tom D. Spies, M.M., associate professor of medicine, University of Cincinnati School of Medicine and director, Nuttman Clinic, Hillman Hospital Birmingham Alabama. 12" cloth 573 pp., with 85 illustrations. Chicago: Year Book Publishers Incorporated 1947. \$3.75.

For twelve years the subject of endocrinology has been published as a part of the *Year Book of Neurology, Psychiatry and Endocrinology*. For 1946 it appears as a new year book associated with metabolism and nutrition. The volume comprises abstracts of important articles printed in English in various periodicals for 1946. Indexes of subjects and authors conclude the volume which is well published in every way. It should prove useful to persons interested in the subjects discussed and desiring to keep abreast of the current literature.

*Microbial Antagonisms and Antibiotic Substances* By Selman A Waksman, M S, D Sc, Ph D, professor of microbiology, Rutgers University, and microbiologist, New Jersey Agricultural Experiment Station Revised edition 8°, cloth, 415 pp, with 33 figures New York The Commonwealth Fund, 1947 \$4 00

Since the completion of the text of the first edition of this book in 1945, great advances have been made in the field of antibiotics Penicillin and streptomycin have become important chemotherapeutic agents The text has been thoroughly revised to bring the subject up to date, and much new material has been added The bibliography comprising 1053 citations has been revised by the omission of many of the historical items contained in the first edition and by the addition of references to the literature to 1946 The book should be in all medical libraries and in the libraries of all persons interested in the subject.

## NOTICES

Dr Robert F Dine announces the opening of an office for the practice of orthopedic surgery at 483 Beacon Street, Boston, and for the practice of bone and joint surgery at 741 Main Street, Waltham

Dr Nathan Louis announces the removal of his office to 171 Bay State Road, Boston

Dr James W Sever announces the removal of his office to 330 Dartmouth Street, Boston

Dr Richard C Webster announces the removal of his office for the practice of plastic and reconstructive surgery to 1101 Beacon Street, Brookline.

## JOSEPH H PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a m

### MEDICAL CONFERENCE PROGRAM

Friday, November 14 — Prolonging the Action of Penicillin

Dr Albert O Seeler

Wednesday, November 19 — Glycogen Storage Disease

Dr Richard Wagner

Friday, November 21 — The Evaluation of Drugs for the Relief of Bronchial Asthma

Dr Maurice S Segal

Wednesday, November 26 — The Discovery of Insulin

Dr Joseph H Pratt

Friday, November 28 — Studies of Certain Metabolic Disturbances Carried Out with the Aid of Isotopes

Dr DeWitt Stetten

On Tuesday and Thursday mornings from 9 00 to 10 00 Dr S J Thannhauser will give medical clinics on hospital cases On Friday afternoons from 2 00 to 4 00 therapeutic conferences will be held with round-table discussion, Dr R P McCombs, Moderator On the second and fourth Friday afternoons of each month, Dr Merrill Sosman will conduct x-ray conferences from 4 00 to 6 00 On Saturday mornings from 9 00 to 10 00, clinics will be given by Dr William Dameshek Medical rounds are conducted each weekday except Saturday by members of the Staff from 12 00 to 1 00

All exercises are open to the medical profession

## GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, November 18, at 8 15 p m A symposium on cancer will be presented, with Dr Joseph C Aub as chairman

## PROGRAM

The Use of the Nitrogen Mustards and Urethane in the Treatment of Neoplastic Disease Dr David A Karnofsky  
Studies in the Chemotherapy of Cancer Dr Arnold Seligman  
Endocrine Therapy of Carcinoma of the Breast Dr Ira T Nathanson  
Stilbamidine in the Therapy of Multiple Myeloma Dr Bernard Jacobson

## SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 18, at 12 noon Dr Charles P Emerson will speak on "Leukemias and Lymphomas"

Physicians are cordially invited to attend

## CUTTER LECTURE

The Cutter Lecture on Preventive Medicine, initiated in 1912, will be given by Dr Haven Emerson, Emeritus Professor of Public Health Practice, Columbia University School of Public Health, on Monday, November 24, at 5 p m, in the Amphitheater of Building D of the Harvard Medical School His subject will be "Whither the Pegasus of Public Health?"

The medical profession, medical and public-health students and others interested are cordially invited to attend

## RADIOLOGICAL SOCIETY OF NORTH AMERICA

The thirty-third annual meeting of the Radiological Society of North America will be held at the Hotel Statler, Boston, from November 30 to December 5, inclusive Symposiums on the economics of medicine, pediatric roentgenology and radioactive iodine will be held on various days of the meeting, and numerous papers concerning the latest advances in x-ray diagnosis and treatment will be presented by members of the society Dr Douglas Quick, of New York City, will deliver the Carman Lecture at 8 p m on Tuesday, December 2

More than 800 members of the society are expected to attend the meeting The scientific program and exhibits give promise of being of great interest The "refresher courses" will be given as usual The commercial exhibits will embrace all the recent and projected developments in diagnostic and therapeutic apparatus An interesting ladies' program has been planned

## NEW ENGLAND HEART ASSOCIATION

The next meeting of the New England Heart Association will be held at the Massachusetts General Hospital on Monday, December 1, at 8 15 p m Dr Paul D White will preside

### PROGRAM

Announcements by the president, Dr Howard B Sprague.  
The Treatment of Intractable Paroxysmal Tachycardia by Sympathetic Block Drs Edward F Bland and J C White

Coronary Arteriovenous Aneurysm A rare anomaly Drs Oglesby Paul, Richard H Sweet and Paul D White.

A Case of Rheumatic Heart Disease with Periodic Arterial Embolism Ambulatory treatment with dicumarol.

Dr Howard B Sprague and Robert P Jacobsen, Ph D

Neurocirculatory Asthenia Drs Mandel E Cohen, Edwin O Wheeler and Paul D White

Phonocardiography and Electrocardiography Drs Howard B Sprague and Bertrand Wells

Unipolar Limb Leads Dr Conger Williams

Interested physicians and medical students are cordially invited to attend

## SUFFOLK DISTRICT MEDICAL SOCIETY

A stated meeting of the Suffolk District Medical Society will be held at the Boston Medical Library on Tuesday, December 9, at 4 30 p m

(Notices continued on page xvii)

# The New England Journal of Medicine

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Number 21

## OCCUPATIONAL DERMATOSES (ERGODERMATOSES)\*

### Diagnosis, Disability and Treatment

JOHN G. DOWNING, M.D.†

BOSTON

**T**WENTY minutes is rather a brief period in which to discuss the large field of industrial dermatoses, but a few thoughts resulting from twenty-five years experience may be of interest. During that time many thousands of workers with cutaneous disturbances have been examined, key industrial plants have been inspected, and lectures have been given to workers, foremen and insurers. Most of the cases considered industrial have been treated, therefore, considerable experience has been gained by trial and error. No set rules have ever been established for the treatment of such dermatoses. The industrial patient must be treated until he is well, there is no reason why he should not recover, because all true occupational dermatoses are curable.

In Massachusetts in 1922 little was known about the effects of industrial exposures, but with the rapid introduction of new chemicals, insurers and industrialists soon learned that the resulting cutaneous disturbances were numerous and expensive. Industry in the Commonwealth has changed in the last twenty-five years. Old industries are gone, and new ones have been installed. Formerly, the leather industry was responsible for a large amount of workers' disability due to occupational dermatoses, later, the rubber industry contributed quite a few cases. The former moved away, and the latter cleaned house. As a result of prophylactic measures, industries formerly notorious for causing dermatoses now have only an occasional worker affected.

The first cases of dermatitis from work with plastics were seen in a small plant in a large field, it is now such a large plant that the field seems small. When this plant was first visited, it was dusty and reeked of fumes. Finished fabricated plastics, being inert, do not cause dermatoses, but the processing of the raw materials produces a considerable number of cutaneous reactions. There is a dangerous

combination of powders, liquids and gases. Although plastics have been made as long as clay has been known, the use of resins resulting from the reaction of phenol and formaldehyde and similar reactions is only thirty years old. The pruritic eruption due to mechanical irritation from the powders has been fairly well eliminated by improved personal hygiene, better washing facilities and the use of protective creams. Education has eliminated skin conditions caused by the careless handling of liquids, which ranged from simple follicular eruptions to severe burns. Lastly, proper sanitation has eradicated not only the helmet-like type of dermatitis on the exposed areas of the skin caused by fumes but also the fine papular eruption resembling prickly heat that appeared on the covered areas, especially in warm weather, owing to penetration through the clothing. There was a constant change of personnel, for whereas many became desensitized, others had to give up this work. Those now affected are new and inexperienced workers.

Lectures accomplish a great deal, but money talks more successfully. Insurers, recognizing the bad risks, drop these policies and the next insurer raises the premium. A worker with an occupational rash is an expensive liability, especially in these days of high-cost hospitalization. Apart from the loss of time and wages of the employe, the compensation and medical expenses may amount to several thousand dollars. A mild eruption may cost at least two or three hundred dollars.

The introduction of patch tests was hailed as the solution to this puzzle (Fig 1). Insurers began to insist on them, commissioners requested them, and patients consented to submit to them. After a decade of enthusiasm, however, patch tests have lost much of their popularity, owing to the number of false or severe reactions (Fig 2). They are now relegated to their proper use—that is, only when indicated. They have their fallacies and limitations, but with a carefully taken history showing definite exposure to the test material, and with a characteris-

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 20, 1947.

†Professor of dermatology, Boston University School of Medicine and Tufts College Medical School.

tic test eruption, a positive finding followed by the prevention of further exposures should result in a cure.<sup>1</sup>

Years ago most workers attributed every eruption to their work. Skilled employes soon realized that alleged industrial hypersensitivities were disastrous, physically and financially, and demanded proof of the causative factor. The physician became more

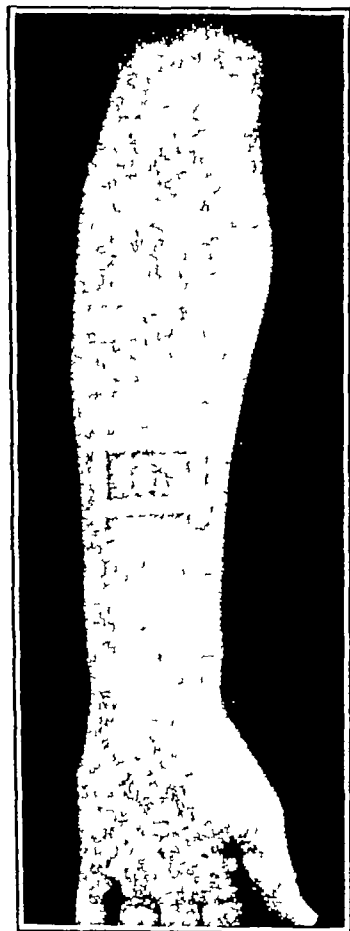


FIGURE 1 Method of Patch Testing<sup>1</sup>

*A piece of linen is moistened with the test substance and covered with Scotch tape that is rimmed with narrow adhesive*

careful in his diagnosis of an occupational dermatitis, for the well paid artisan is apt to resent any loss of pay when it is proved that his eruption is not due to his work but is constitutional in origin or is due to contacts at home, especially when industrial commissioners so rule against him. With the recent increase in wages, workers became suspicious of snap diagnoses, and it is amazing how many continued to work despite their occupational eruption and were relieved without loss of time.

Despite the tremendous increase in industrial activities during World War II, the increase in dermatoses was not excessive in this part of the country, except in the incidence of infection due to cutting

oils. The increase occurred for the most part in plants transformed overnight into machine shops. The incidence of claims for industrial dermatoses is an excellent index of industrial productivity. For the past two months there have been more claims than in any two months when wartime activities were at their height.

### DIAGNOSIS

What establishes the diagnosis of an occupational dermatosis? In 1939 the Committee on Industrial Dermatoses of the American Medical Association<sup>2</sup> adopted the following definition: "An occupational dermatosis is a pathological condition of the skin for which occupational exposure can be shown to be the major causal or contributory factor." The same committee submitted the following criteria, which usually apply in the majority of cases of occupational dermatoses:

The dermatologic diagnosis is that of a dermatosis in which the role of an occupational causal (major or contributory) factor has at some previous time been established beyond reasonable doubt.

The patient has been working in contact with an agent known to have produced similar changes in the skin.

The time relation between exposure to the agent and the onset of the dermatosis is correct for that particular agent and that particular abnormality of the skin.

The site of the onset of the cutaneous disease and the site of maximum involvement are consistent with the site of maximum exposure.

The lesions present are consistent with those known to have followed the reputed exposure or trauma.

The patient is employed in an occupation in which similar cases have previously occurred.

Some of the fellow workers using the same agent are known by the examiner to have similar manifestations from the same cause.

So far as the examiner can ascertain there has been no exposure outside the occupation that can be implicated.

If the diagnosis is dermatitis, the following items are important: attacks occurring after exposure to an agent, followed by improvement and clearing after cessation of exposure, constitute most convincing evidence of the occupational factor as a cause, and the results of patch tests performed and interpreted by competent dermatologists corroborate the history and the examination in the majority of cases.

These criteria, however, are rather complicated and do not apply to cases in which there is aggravation of an existing cutaneous disease by industrial exposure. Nor do they apply to the large number

of cases in which the disabling eruption has resulted from treatment by the plant physician or nurse with a sensitizing medicament or has been caused by overtreatment

#### MEDICOLEGAL ASPECTS

In Massachusetts the legal definition of occupational dermatosis seems more clear-cut. It is any injury, damage, harm or disease of the skin that arises out of and in the course of employment.<sup>8</sup> Such an injury is compensable if it causes incapacity

Cases of occupational dermatoses are so complicated that the Massachusetts Industrial Accident Board will not accept an opinion unless it is expressed by a duly qualified physician. What makes these decisions so difficult? It is because few have the training that enables them to assemble all the parts and solve the problem. A physician must have dermatologic training to distinguish between the occupational and the nonoccupational dermatoses. In reviewing many thousands of cases of workers presenting claims, I found about 40 per cent to be

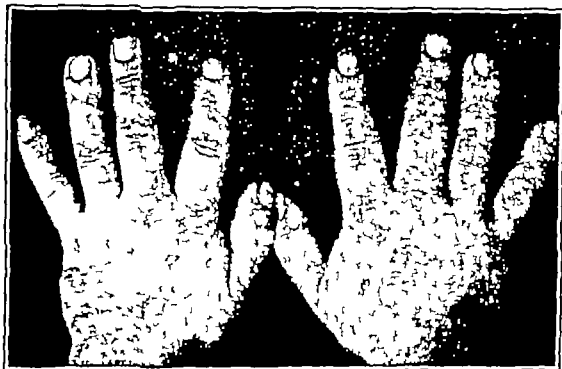


FIGURE 2. Case of J. T., a Candy Maker (Dermatitis from Contact with Cinnamon Oil)

The patch test resulted in a generalized dermatitis

and takes away a worker's ability to earn wages. Disease is not compensable unless it arises from an injury, and although dermatitis is considered a disease, definite injury must be established before a claim is accepted. These facts are simple but are misinterpreted, not only by the general practitioner but also by the dermatologist. A recent article written by a dermatologist stated that miliana was considered occupational if the weather was hot (Miliana is an acute affection of the sweat glands that occurs in many persons in hot weather, regardless of whether or not they work). A new industrial commissioner dreads a case of dermatitis, and few private lawyers have any understanding of the Compensation Act or of the court decisions regarding it. Many a plaintiff would have lost his claim except for a sympathetic commissioner. These officials are admittedly slightly partial to the employee, and perhaps justly so. To the insurer and its representatives, either lawyers or physicians, it is just another case, the loss of which will not in any way change their routine. To the injured worker it is a tragic, all absorbing controversy, the solution of which may determine his future and that of his family.

nonindustrial, comparatively few of these opinions have been disputed. Correct dermatologic diagnoses save employers, insurers and employees many thousands of dollars. A knowledge of occupational exposures is essential, including the chemicals used and the processes involving their use. A knowledge of the sanitary conditions in a particular plant is helpful. For example, fungous infection of the feet is not considered industrial, but, if a man is constantly working on a wet or damp floor so that his shoes and socks are always wet, an ideal condition is produced for the growth of yeast and fungi and could be a precipitating factor in a disability that later results from this infection.

Thorough examination of the claimant is essential. The sites first affected and the characteristics of the eruption should establish a definite diagnosis of an occupational dermatosis. These facts are few, but each one has its own importance in the expression of an opinion. The physician needs no vast knowledge of chemistry or sanitation to gather all his data, because on request the insurer as a rule will supply this information, if not, the various state agencies are willing to assist him.

There are a large number of cases in which the worker acquires a superficial injury of the skin, such as a paper cut, abrasion or friction burn, and later suffers a pyogenic infection at this site, showing a sharply outlined vesicular and pustular eruption that is resistant to treatment and subject to frequent relapses. These cases are often mislabeled "fungous infection" owing to failure to obtain a history of injury or cultural studies, and the worker is refused compensation. The largest group, however, comprises patients overtreated or treated with medication to which they have a hypersensitivity. This medication was formerly a mercury compound, later the sulfonamide group, and next penicillin, and I have recently seen 2 cases resulting from the use of Furacin. These drugs should not be em-

ployed in occupational dermatoses unless there is infection, and then with caution and only until the secondary infection is relieved, when bland medication should be substituted.

alkalies, metals, salts, essential oils, solvents and miscellaneous substances.<sup>5</sup> In this large group of cases, the history should reveal the causative factor, because patch tests are unnecessary. Primary irritants should not be used in patch testing. Again, most of the workers suffering from the above conditions can continue to work unless the eruption is severe, when it has disappeared, there is no reason why they should not return to their previous occupation.

It is essential to distinguish between primary skin irritants and sensitizers, frequently called "aller-

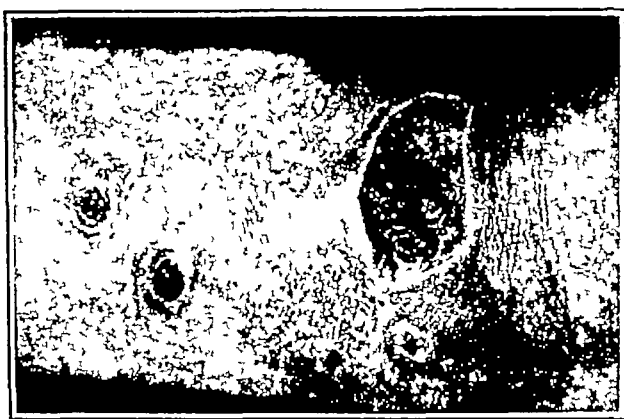


FIGURE 3 Case of S D, a Leather Seasoner (Chromic Acid Burns)

*The lesions (seen in tanners, masons and plasterers) show an elevated rim of whitish-gray skin with a central dark ulceration resembling a pigeon's eye, and hence called "pigeonneau".*



FIGURE 4 Case of J S, a Leather-Heel Trimmer  
Sensitization produced an eruption simulating nummular eczema

#### HYPERSENSITIVITY

The majority of true occupational dermatoses are due to primary skin irritants. In 1936 the committee mentioned above defined a primary irritant as follows: when a substance in a given concentration, in a given vehicle and in a given manner and length of exposure produces a clinically manifested irritation on the skin of a majority of persons not previously sensitized to that substance, that substance is a primary irritant under the specified conditions.<sup>2</sup> Irritants may cause lesions ranging from erythema to deep necrosis of the skin (Fig 3). Primary irritants can comprise mechanical and physical agents and powerful chemicals, including acids,

alkalies, metals, salts, essential oils, solvents and miscellaneous substances.<sup>5</sup> The Committee on Industrial Dermatoses has defined a sensitizer as one that increases the capacity of the tissue to react to subsequent exposure. In my experience hypersensitivity to a single allergen occurs in only a few industries. This group of sufferers constitutes the chief problem in occupational dermatology. A carefully taken history of any previous cutaneous disease is most important, in my experience, about 7 per cent of patients have had previous attacks.

Primary irritants that are also sensitizers are essential oils, acids (carbolic, chromic and oxalic), alkalies, soap, cement, lime, various salts — such as the chromates, sulfates, arsenates and nitrates — solvents and the miscellaneous group previously mentioned (Fig 4). The variation of the incuba-

tion period is misleading it may range from several days to many years. In this group patch tests may be of value, and the patient usually has to seek other employment. The longer the incubation period or time of exposure, the greater the sensitization and the more difficult the cure, because these patients become polysensitized. Therefore, medication must be carefully selected, outside activities curtailed, the use of soap and water prohibited and even a dietary regime imposed, for the use of stimulants and improper diet prolongs the disability. The onset is slow and insidious, and the skin frequently presents a somewhat characteristic appearance, except for the hypersensitivity, there is no permanent stigma, such as scarring. This hypersensitivity does not remain specific.

The workers become subjects of controversy before industrial-accident boards for the rest of their occupational existence. They are the ones told not to return to their previous occupation and to avoid exposure to wet work and the use of soap and water — in other words, to refrain from some of the normal activities of life. By law, this hypersensitivity is not compensable, the worker must seek other employment and avoid the substance that might produce a new attack. If this new attack occurs at home or under self-employment, there is no redress, if it occurs while he is working for a new employer, the responsibility for medical care and compensation rests on him. If the worker testifies under oath that some traces of the original eruption remain over a period of several years, the original employer or his insurer is responsible. It sounds simple, but clever lawyers can make the rendering of an impartial decision extremely difficult. The injured employee listens, dazed with the conflicting testimony. He may, however, amaze the attending physician, employed by the insurer, who, properly proud of having cured a difficult eruption, has to listen to criticism of his efforts and accusations against his integrity. The timely use of soap and water or chemicals or friction just before the hearing is sometimes a matter of consternation to the attending physician, who a few days or weeks previously had reported that the patient was well. During the war these cases were extremely rare, but now they are increasing and occur mostly among female workers who have returned to the role of housewives or who have married and find the compensation a useful adjunct to the household budget. Perhaps there is some justification for their position, but we must realize that the largest group of occupational dermatoses is among housewives, who comprise nearly 30 per cent of my private practice, practically all these cases are due entirely to household activities, exposure to soap and soap powders, squeezing oranges, handling raw vegetables and fruit, canning and many of the other activities of the active mother (for 95 per cent of these women have children). These are persons who have never had outside industrial con-

tacts, so that it is just as probable that the plaintiffs were victims of their own household exposures. I believe that the proper way to dispose of these cases would be a reasonable lump-sum settlement, for as O'Donovan<sup>6</sup> states there is nothing more curative than the golden ointment of compensation.

Characteristic lesions may appear from exposure to these sensitizers or allergens, producing the so-called "allergic dermatitis" or eczema. These are inflammations of the skin due to repeated exposure to substances that are normally innocuous (Fig. 5).



FIGURE 5 Case of H. M., a Shoe Dresser

*Eruption frequently seen in shoe dressers and tanners from contact with irritating chemicals*

Chlorinated hydrocarbons usually produce characteristic mechanical and follicular plugging with comedones and cysts, but occasionally an allergic reaction consisting of a diffuse erythema is seen on the face, hands and arms of chemists after repeated experimentation. This erythema fades, the skin desquamates, and finally the characteristic comedones and cysts appear as the result of condensation of chloro compounds in the follicles. A similar combination of mechanical or primary irritation and sensitization reaction is seen in workers who use soluble cutting oils. The sensitization is due to the sulfuric acid and the preservatives in the oils.

Resins and sensitizing dusts frequently cause symptoms and signs similar to those produced by cosmetics, such as face powders and nail polish.



There is itching of the eyelids and the sides of the neck, later, other parts of the exposed skin become affected. The skin is dry, red and scaly, and continued exposure causes edema of the eyelids. As the patient becomes more sensitized the edema appears, and fine papules and vesicles are superimposed.

Workers whose hands are constantly wet develop maceration of the interdigital skin and a sensitivity to the chief ingredient in the solution, whether it is soap, a fruit or a vegetable. I have seen positive patch-test reactions from carrots, lettuce and tomatoes. These eruptions usually start in the webs of the fingers and spread over the backs of the hands and on to the anterior aspect of the wrists. There is a "boiled-out" appearance of the interdigital interspaces, with erythema and vesiculation of the remaining areas. The eruption rarely spreads beyond these areas unless overtreated, and is usually complicated by secondary infection, such as pyogenic bacteria or yeastlike organisms.

Sensitivity to chromates and bichromates, which may be polymorphous in character, presenting oval or round patches, is frequently seen in shipyard workers in contact with a dull-green paint. These patches are described by Hall,<sup>7</sup> who attributes them to contact with the zinc chromate primer in the paint. He was able to differentiate the eruptions from zinc chromate and those from resin. The latter causes a dermatitis on the sides of the neck, consisting of oval, dull-red, finely squamous, palpable plaques whose long axes are parallel to the lines of cleavage of the skin, as in pityriasis rosea, whereas the former causes nummular and eczematous plaques. The most interesting eruption was one seen at the beginning of the recent war among the enlisted personnel in the Navy and Coast Guard. It appeared on the dorsa of the hands, near the wrists, and on the outer lateral aspects of the extremities. The primary lesions were vesicles, which later became grouped, forming elevated, circular, red, vesicular and oozing patches that tended to clear in the center. These eruptions resembled nummular eczema and were frequently so diagnosed. Patch tests proved that they were caused by the cloth of the uniform, due to a bichromate used as a mordant. A similar eruption appeared among stitchers of this cloth.

Workers highly sensitized to gasoline may show a generalized eruption consisting of erythema and patches of grouped vesicles similar to a dermatitis herpetiformis. Male workers in garages and places where there are poor working conditions, such as dirty floors, frequently present eruptions that start on the dorsa of the feet and about the ankles, spreading up the legs. Rubber finger cots may cause an intensely pruritic, pink, scaly eruption at the site of contact, and heavy rubber gloves may cause a colorless, fine, papular eruption. Dye may produce nothing but an intense edema followed by desquamation. Even the most expert diagnosticians, however, can-

not depend alone on observation, for most contact eczemas are similar in appearance, and a complete history and patch testing are usually necessary to prove the original cause. When other cases result from the same exposure, the cutaneous disturbance is readily recognized. Experience is the best teacher.

### DISABILITY

All insurers' medical reports request that the physician express an opinion regarding disability—whether it is total or partial, permanent or temporary. What constitutes disability? The insurer recognizes the fact that if an injury occurs in the course of employment and produces an extensive dermatitis, the worker is temporarily totally disabled. When the accomplishments of blind veterans and those without limbs are considered, however, it seems incongruous to state that the dermatitis of the right index finger of the maker of rubber coats is totally disabling. But this injury destroys his earning capacity, for his work is done chiefly with this finger, by union regulations he is allowed to do no other work, not even to use a brush.

If a stenographer suffers a slight abrasion on the hand from the corner of the desk, the injury is not disabling and hence not compensable. If, however, the plant nurse applies a sulfonamide and the hand becomes swollen so that the patient is unable to type, she is entitled to compensation. If on a warm summer day, with her employer's permission, she eats lunch on the premises of the plant and suffers on her legs a dermatitis from poison ivy, or if she takes a short cut through the plant grounds and suffers intense swelling of the legs so that she cannot get to work, she is entitled to compensation. The same situation in a neighboring field, however, is not recognized as arising out of or in the course of employment and is therefore not compensable. The eruption on the fingers of a soda-fountain clerk is not totally disabling, because she can be put on dry work and treated without loss of time.

The disability from a true occupational dermatitis is never permanent, except for hypersensitivity, because all such dermatitides are curable. It has been ruled by the Massachusetts Supreme Court that sensitivity is not compensable, the worker must seek other work.

A disfiguring scar or a repulsive chloracne of the face lessens the worker's earning capacity in the labor market, and he should therefore be compensated, irrespective of his ability to work. In the Fennell case the employe sustained an injury to the left eye resulting in total loss of vision in that eye, and in such a change in appearance from the right eye that in turning the left eye its abnormal condition was apparent. Despite his testimony that he could do his work better after the accident because he was more careful, he was awarded compensation. The Industrial Accident Board concluded that total inability to do work and total in-

capacity to earn wages for work done are not synonymous, and that total incapacity is present if the employee in the case at bar, on account of the appearance of his eye, is unable to obtain work. Compensation is allowable when there is an impairment of earning capacity. When an employee is disabled from doing some kinds of work and is unable to obtain work of the type he is able to do, a finding of total incapacity is warranted (*Sullivan* 218 Massachusetts 141). On principle, when a worker is unable to obtain other employment because of visible, physical results of an industrial accident, his earning capacity is as much impaired as if he were physically disabled to the extent that he could do no work (*Fennell* 289 Massachusetts 89, 1935).

Statutes in many other states provide payment for disfigurement, without evidence that it results in loss of earning capacity, but in a few states, including Massachusetts, there is no such provision, and only when it interferes with earning capacity can disfigurement be made the basis of an award. In *Streeting v. American Knife Company* (226 New York 199, 1919), in which an explosion disfigured the employee's nose and face, the New York court held that "serious facial disfigurement has a tendency to impair the earning power of its victims," although in New York payment is provided, by statute, for disfigurement. Courts and industrial accident boards recognize the difficulty encountered by the maimed, crippled or disfigured employee. An actress or waitress left with repulsive scars, preventing her from obtaining employment, has lost her earning capacity as much as if she were actually bedridden. As a matter of fact, the Pennsylvania Court, in *Naughton v. Keil* (154 Pennsylvania Superior Court 318, 1944) and in *Eckley v. Roe* (128 Pennsylvania Superior Court 577, 1937), followed this theory, and in the latter case stated specifically, "It is a matter of common knowledge that there is a general disinclination on the part of employers to give work to cripples."

Bear<sup>2</sup> cites a case tried before the Industrial Accident Board, that of *Lillie Hendricks v. Chesterfield Laundry Service Company*. This employee was a thirty-one-year-old Negress who was operating a laundry pressing machine. A part of the machine weighing about 50 pounds shut down on her right forearm, burning her. She managed to free herself and then fainted. In treatment, a dye that formed a firm eschar over the wound was used. It slowly loosened around the edges, and for a time a new dye was applied to the raw areas. As the coagulum was gradually removed ointment was applied, until finally a granulating surface was obtained. The large open surface was then filled in with skin grafting. This graft took fairly well, except that where it crossed the wrist joint there was some stiffness and cracking due to the motion of the joint at that point. The important feature of the case, however, was that the patient was left with an

extensive keloid formation, which disfigured her arm. The employee testified at the hearing that she was sent from an employment agency to two different families to do housework. The prospective employers kept looking at her arm, and the agency was notified after each interview that she had not been hired because the scar was considered obnoxious. The Commissioner found that this constituted a disability and awarded compensation, which the insurer paid without appeal to the courts.

### TREATMENT

Treatment of occupational dermatoses begins with the elimination of the causative factor. The ideal method is that of prevention, achieved in the first place by not allowing a potential hazard in the industrial process. Such elimination will never be possible in industry, however, because there will always be essential chemicals that affect a certain number of workers. These possible irritants or sensitizers should be properly labeled so that due precaution against harmful reactions can be taken. Education of the worker regarding care in handling such substances and the installation of facilities for the proper method of cleansing the skin after work are invaluable. Many workers have sustained eruptions from using gasoline, thinner, turpentine or harsh soaps on the skin to remove the day's grime. Supervision is necessary, because workers are apt to refuse to work with gloves or will take unnecessary short cuts in their work, and carelessness causes considerable trouble. A chemist was seen who extracted cashew-nut-shell oil, a notorious primary irritant and sensitizer. During the process of extraction he was careful, wearing a mask, protective clothing and gauntlet rubber gloves, but when the extraction was completed he thoughtlessly discarded them and washed the utensils with his bare hands with a resulting dermatitis.

Early and correct diagnosis of an occupational eruption is most important. If the exact causative factor is easily recognized, removal of the hazard or protection of the worker from any possible contact, together with soothing applications, may be sufficient to prevent disability. If the worker is new on the job an attempt should be made to keep him on it, for if he can survive the first few weeks he may become more or less immune, as many have done. Such workers should be kept under close observation and removed from the work if the eruption spreads.

Twenty-five years of practice in industrial dermatology has produced experience that frequently clashes with papers and books on the subject of returning to work. Records in my office on industrial patients observed over a period of twenty years show that about 50 per cent returned to their old jobs. By exercising due care they were able to work for periods ranging from one to five years without a new attack, and the new attack fre-

quently followed an illness or a vacation. One baker has lost no time despite periodic attacks of baker's eczema for over ten years. His sensitivities have varied, at one time being due to the improver, at another to cinnamon and later to a combination of salt and lard. At times the face, hands and arms have been involved, but the eruption has never spread to other parts of the body. Other patients who previously presented occupational dermatoses have returned to my office with other forms of eruption, such as sensitization due to medication used in the treatment of trivial injuries, or secondary infection following a slight break in the skin.

Many occupational dermatoses arise not from the occupational exposure alone but from a combination of factors, examples of such patients are the man who paints at work and also at home, and the waitress who works all day and then does her housework. Many occupational dermatoses would not occur but for some intervening factor such as those just mentioned, intercurrent illness and internal medication, excessive fatigue or neglected injuries to the skin. These lower the threshold of resistance, and when the patient is relieved and these factors have been eliminated, the threshold rises and many workers can resume their work with impunity.

Anderson<sup>8</sup> elaborates on a suggestion made several years ago: the use of mild soothing solutions with a slight increase in the reaction in the presence of acids and a decrease in the presence of alkalis.<sup>10</sup> He states that four different points of attack can be applied to the problem of chemical neutralization of a cutaneous irritant. In the first place, direct chemical neutralization may be used, a corrosive and irritant alkali can be neutralized by a weak acid, such as acetic acid (vinegar) or citric acid (lemon juice). The same principle is involved in the use of weak alkalis in the neutralization of irritant acids. Secondly, one may detoxify the chemical irritant by another chemical, which reacts to form an insoluble or nonirritating compound. Thus, chromium compounds can be oxidized into innocuous metallic salts by sodium sulfite. Thirdly, the chemical phenomenon of absorption may be employed. Medications based on this phenomenon are the absorbent powders, such as charcoal and kaolin. Finally, the unusual emulsifying and detergent properties of the new synthetic wetting agents may be used to remove toxic chemicals from the skin. These suggestions are valuable if the causative factor is recognized immediately and the proper treatment is instituted. If a neutralizing solution is not available, plenty of water will dilute the irritant.

Wet dressings should be the first topical remedy. A 5 per cent solution of sodium hyposulfite, either hot or cold, is used in the treatment of poisoning from dyes and chromates. Wet dressings of physiologic saline solution are soothing. When there is only redness and swelling, a saturated solution of magnesium sulfate will produce quick results. When

the skin is red, swollen and vesicular, a 5 per cent solution of aluminum acetate or 2 per cent solution of boric acid, either separately or combined, is extremely valuable, antipruritic and cooling and permits proper drainage. These dressings should be composed of heavy gauze or strips of Turkish towel-ling that have been boiled. They should be changed frequently to remove the debris and allow evaporation. Wet dressings of boric acid, citric acid or citrates may be applied to the so-called "cyanide rash" occasionally seen in jewelers. In the acute stages of cutting-oil folliculitis, the use of wet dressings of 25 per cent isopropyl alcohol has been beneficial. Potassium permanganate in a 1:4500 solution and 0.125 to 0.25 per cent of silver nitrate may be employed when there is secondary infection. Boiled milk (four parts) and lime water (one part) are soothing in cases of dermatitis about the orbits and sides of the neck, such as occurs from exposure to irritating dusts, fumes and resins.

Powders cool and dry the skin, and while protecting it from external irritation permit heat radiation. The combination of alternate wet dressings and dusting of the surface with powder quickly relieves the congestion. The mineral powders are better than the vegetable. The former—kaolin, bismuth compounds, magnesium and calcium carbonates, zinc oxide and zinc stearate—are absorptive and clean and are valuable when there is considerable weeping. Vegetable powders should be used only in combination with mineral powder, because of their tendency to swell and decompose. Wet dressings alone should not be applied for more than twenty-four to forty-eight hours, because they cause maceration. The combination of wet dressings and powders should not be employed for more than seventy-two hours.

If powders are used too long, they tend to clog and to interfere with secretions so that reactions of hypersensitivity or autosensitization appear, or they predispose to pyogenic infection, with the formation of intrafollicular pustules or lymphangitis.

If there is no marked redness or swelling, lotions may be applied immediately or within twenty-four hours. For a universal standby, Calamine Lotion (*National Formulary*), with 1 per cent phenol, is useful, but the physician should not limit himself to a single prescription, for as each eruption and skin varies, so should the local application. Properly prescribed and applied, lotions produce the best results and testify to the therapeutic skill of the physician, the pharmaceutical ability of the chemist and the training of the nursing attendant. Careful directions should accompany the prescription. Being a suspension of powder in fluid, it should be shaken well and spread or evenly sprayed over the skin. A soft paint brush or spray gun is advantageous when the surface is extensive. Glycerin is valuable because of its power to absorb moisture, but it retains the moisture and therefore should be

omitted in cold weather, because it makes the skin feel cold and sticky. I have used the formulas\* referred to below in the treatment of various occupational dermatoses. When there is considerable secretion and danger of infection from the nature of the work (such as sensitization from soluble cutting oils), the following formula is useful:

SUBSTANCE	AMOUNT
Calamine	20 gm
Zinc oxide	20 gm
Boric acid	10 gm
Glycerin	1 cc
Bentonite	2 gm
Lime water (as needed) to make a solution of	20 cc

Bentonite is a colloidal clay that acts as a medium for suspending the powders in the liquid by producing a gel. For the erythematous, squamous eruption, such as that seen after contact with irritating dusts, fumes or resins, the following may be used:

SUBSTANCE	AMOUNT
Phenol	2 gm
Zinc oxide	10 gm
Calamine	10 gm
Starch	30 gm
Glycerin	10 cc
Distilled water (as needed) to make a solution of	250 cc

When there is marked pruritus, additional antipruritics may be added, such as the following:

SUBSTANCE	AMOUNT
Menthol	0.6 gm
Phenol	1.2 gm
Solution of coal tar	8.0 cc
Calamine lotion (A-F as needed) to make a solution of	200 cc

Coal tar solution is much more satisfactory for the preparation of lotions and liniments if made with 70 per cent alcohol instead of 95 per cent. The addition of the cut-colored neocalamine in sufficient amount to match the patient's skin makes a more pleasing preparation. Neocalamine, however, stains clothing and bed linen. For the relief of an intensely itchy follicular eruption, seen after contact with rubber or mica, when there is no evidence of infection, the following lotions are valuable:

SUBSTANCE	AMOUNT
Menthol	0.6 gm
Phenol	1.2 gm
Solution of coal tar	10.0 cc
Zinc oxide	20.0 gm
Talc	20.0 gm
Glycerin	15.0 cc
Alcohol (35 per cent, as needed) to make a solution of	250.0 cc
Menthol	0.5 gm
Solution of coal tar	15.0 cc
Glycerin	10.0 cc

\*Many of these formulas were developed with the collaboration of Louis A. Osmann and Mitchell J. Stoklosa, of the Department of Pharmacy, Massachusetts College of Pharmacy, Boston.

Witch hazel	100.0 cc
Solution of boric acid (as needed) to make a solution of	240.0 cc
Solution of coal tar	2.0 cc
Phenol	2.0 gm
Menthol	0.3 gm
Boric acid	3.5 gm
Witch hazel	100.0 cc
Alcohol (70 per cent, as needed) to make a solution of	250.0 cc

Isopropyl alcohol, being much less expensive, can be substituted for the alcohol.

The following is an old reliable prescription for dry, chapped hands and fingers:

SUBSTANCE	AMOUNT
Tincture of benzoin	15 cc
Glycerin	10 cc
Rose water (as needed) to make a solution of	250 cc

When the lips become chapped and fissured, bathing with the following is beneficial:

SUBSTANCE	AMOUNT
Sodium borate	6 gm
Tincture of myrrh	20 cc
Water (as needed) to make a solution of	250 cc

When the skin becomes crusted, it should be bathed with equal parts of a 2 per cent solution of boric acid and a 10 per cent solution of aluminum acetate until the crusts soften and become detached. They should not be removed forcibly. Pastes are then indicated, the acute inflammation having subsided. Their action is more prolonged and protective, and they adhere to and soften the scales and crusts.<sup>11</sup> A paste is a rather stiff preparation consisting of powders and the vehicle, which may be glycerin, hydrocarbons, paraffin, petrolatum or animal or vegetable fats. Those containing glycerin are watery pastes, such as the following:

SUBSTANCE	AMOUNT
Starch	12 gm
Distilled water	24 cc
Glycerin (as needed) to make a solution of	120 cc
Zinc oxide	30 gm
Talc	30 gm
Glycerin	30 cc
Distilled water	30 cc

The most popular pastes are those having a base of petrolatum, such as the official paste of zinc oxide containing equal parts of zinc oxide and powdered starch and 50 per cent of fat. On hairy surfaces, zinc oxide is apt to cause a folliculitis, in which event its proportion should be reduced. The following formulas are suggested:

SUBSTANCE	AMOUNT
Zinc oxide	2 gm
Starch	15 gm
Petrolatum	15 gm
Solution of aluminum acetate	10 cc
Lanolin	30 gm
Zinc oxide paste	30 gm

If itching persists in this subacute stage, one of the antipruritic lotions should be applied before the paste

To avoid the necessity of two topical applications, a mixture of lotion and oil — that is, a liniment or emulsion — is used. Calamine Liniment (*National Formulary VII*) and Neocalamine Liniment (*National Formulary VII*) are excellent examples

SUBSTANCE	AMOUNT
Prepared calamine	15 gm
Zinc oxide	15 gm
Olive oil	125 cc
Solution of calcium hydroxide (as needed) to make a solution of	250 cc
Prepared neocalamine	30 gm
Olive oil	100 cc
Solution of calcium hydroxide (as needed) to make a solution of	250 cc

Mineral oil may be substituted in the above prescriptions if, as sometimes happens, the patient is hypersensitive to olive oil or because of its shortage or expense. Various antipruritics can be added

SUBSTANCE	AMOUNT
Solution of coal tar	8 cc.
Calamine liniment ( <i>N E VII</i> , as needed) to make a solution of	250 cc

If there is any evidence of pyogenic infection the following formula can be prescribed

SUBSTANCE	AMOUNT
Menthol	0.5 gm
Phenol	1.0 gm
Ichthammol	7.5 gm
Zinc oxide	30.0 gm
Olive oil	100.0 cc
Lime water (as needed) to make a solution of	250.0 cc

In prescribing liniments other than those of the *National Formulary*, it is well to advise the pharmacist to use an electric mixer. Wetting agents, such as sodium lauryl sulfate, are valuable additions to liniments. Their effectiveness is based on their power to reduce surface tension between the solid and the solvent, thus permitting penetration and dispersion of the solid. The following formula is smooth and efficient

SUBSTANCE	AMOUNT
Zinc oxide	15.0 gm
Calamine	15.0 gm
Olive oil	60.0 cc
Sodium lauryl sulfate	5.0 gm
Phenol	0.5 gm
Water (as needed) to make a solution of	250.0 cc

In persistent infiltrated extensive areas in which there is no evidence of infection, tar is useful, but it should be employed sparingly and only in the late stages. Liniments are of most benefit in an extensive eruption due to sensitization when the vesiculation has ceased, the crusts have become detached and the skin is red, dry and pruritic — that is, after the acute stage has subsided

The majority of occupational dermatoses should be cured by the use of wet dressings, lotions and, finally, pastes and emulsions. Creams and ointments cause many of the complications of the treatment of occupational dermatoses. Ointments, especially, having no evaporating properties and being comparatively free from water, cause irritation and congestion when used in the initial stages. They may be employed in the subacute stage or in persistent eruptions. Neocalamine and Calamine Ointment (*National Formulary VII*) are excellent preparations. In fact, if physicians would prescribe more ointments of the *National Formulary*, they would have more expertly compounded prescriptions and less sensitization. When ointments contain drugs such as phenol, mercury, resorcin, Furacin and benzocain, the sulfonamides and penicillin, there is danger of absorption or sensitization. If there is no infection, there is no indication for their use. If secondary infection occurs, these drugs may be employed with caution and rarely for over one week, for by that time the infection should be relieved.

Ordinarily, an occupational dermatosis needs no internal therapy. When there is secondary infection, however, a sulfonamide or penicillin may be indicated. I prefer 50,000 units of penicillin in physiologic saline solution intramuscularly every three hours, it should be given no longer than five days, because that period is usually sufficient and sensitization is avoided. A dosage of 300,000 units of penicillin in wax and peanut oil daily is also useful, but the possibility of sensitization is increased by allergenic properties of the peanut oil. Benadryl and Pyribenzamine should be given during the period of injection. They have been helpful in controlling the spread and itching in the sensitization type of occupational dermatoses. If the patient is working, Benadryl should not be given because of its tendency to cause drowsiness. I prefer Pyribenzamine, which seemed to be of value in a few cases of industrial dermatitis. Autohemotherapy, alone or combined with previous intravenous injections of calcium gluconate, apparently helps when there is considerable edema or rapid extension of the eruption.

Some readers may criticize this array of formulas. Everyone knows that a normal skin may prefer one soap to another, usually owing to the difference in the reaction or to the amount of free alkali present, or a woman may try a dozen face powders before she finds one suitable to her skin. How much more important is topical application prescribed for the injured or traumatized skin! Frequently, a patient states that irritation or no relief resulted after the use of calamine lotion, but when she is persuaded to use the same lotion modified by the addition of boric acid, talc or starch or coal-tar solution, an immediately soothing response is obtained. A resourceful and successful therapist must have many topical applications at his com-

mand to obtain results in treating the various dermatoses. Expert knowledge of the medication and methods of using a few prescriptions is all that is necessary for the majority of cases, but it is the few that try one's patience and test one's therapeutic ability. With removal of the cause and with proper treatment and proper co-operation on the part of the patient, all industrial dermatoses can be cured.

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Two and a half centuries after Ramazzini described the case of a young gilder who died from mercurial poisoning from inhalation, I saw a fatal case in a young woman — a pioneer worker in a new industry — who died from such exposure. That exposure has been eliminated after loss of a human life, which might have been prevented if the manufacturers had known of the danger of mercurial poisoning and had taken precautions against it.

Severe injuries have resulted from the use of x-rays in industry. Their use has been continued, but proper precautions are taken to prevent harmful effects. So, too, with the introduction of new processes as a result of the discovery of the atomic bomb. Today, practically all known elements can be made temporarily radioactive by means of the cyclotron. Proper medical supervision by industrial experts

may prevent serious industrial dermatoses such as cancer of the skin, which is one of the aftermaths of excessive exposure to radiation.

The general practitioner cannot be expected to keep abreast of the rapid changes in industrial chemistry and physics, such as the radioactive substances. He must necessarily rely on industrial experts for information. With the vast amount of literature on medical therapy, however, he should know the indications and method of use of recent antibiotics and drugs.

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## THE HEPATITIS OF HYPERTHERMIA

### Report of a Fatal Case

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BOSTON

**PATIENTS** receiving intensive artificial fever therapy occasionally develop jaundice. This phenomenon has recently been reported as a major complication of therapeutic hyperthermia by several different groups of observers.<sup>1-3</sup> In the reported series the incidence of jaundice has been as high as 19 per cent.<sup>4</sup>

The jaundiced patients follow a characteristic clinical course. Usually within the first twenty-four hours following fever, exaggerated nausea and vomiting occur. Within forty-eight hours the urine is dark and jaundice becomes apparent. There may be upper abdominal discomfort and tenderness over the liver. Fever, if present, is slight. In the great majority of cases the jaundice promptly disappears, usually within a week, and the patient rapidly recovers from the accompanying symptoms.

Although there is general agreement that the jaundice is the result of liver damage rather than of excessive blood destruction, divergent opinions

have been expressed concerning the pathogenesis of the underlying hepatic disorder. The theory propounded by Brown et al.<sup>4</sup> — that inadequate replacement of salt and water is chiefly responsible for the jaundice — is widely held by those using artificial fever. MacDonald<sup>2</sup> suspected the sulfonamides, which are frequently administered simultaneously. More recently speculation has centered on the possibility of a virus etiology.

Descriptions of the histopathology of the liver could be found in only 2 cases, presumably because the syndrome is rarely fatal. Both descriptions are brief and lack illustrations. Wilbur and Stevens<sup>5</sup> reported their findings in a patient who received artificial fever therapy, developed jaundice and died on the third day after treatment, the liver weighed 2350 gm and showed a diffuse early necrosis. Chunn and Kirkpatrick<sup>6</sup> described a similar case in which death occurred on the fourth day after fever and examination revealed a liver weighing only 1320 gm and showing extensive atrophy.

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If itching persists in this subacute stage, one of the antipruritic lotions should be applied before the paste

To avoid the necessity of two topical applications, a mixture of lotion and oil — that is, a liniment or emulsion — is used. Calamine Liniment (*National Formulary VII*) and Neocalamine Liniment (*National Formulary VII*) are excellent examples

SUBSTANCE	AMOUNT
Prepared calamine	15 gm
Zinc oxide	15 gm
Olive oil	125 cc
Solution of calcium hydroxide (as needed) to make a solution of	250 cc
Prepared neocalamine	30 gm
Olive oil	100 cc
Solution of calcium hydroxide (as needed) to make a solution of	250 cc

Mineral oil may be substituted in the above prescriptions if, as sometimes happens, the patient is hypersensitive to olive oil or because of its shortage or expense. Various antipruritics can be added

SUBSTANCE	AMOUNT
Solution of coal tar	8 cc
Calamine liniment ( <i>N E VII</i> , as needed) to make a solution of	250 cc

If there is any evidence of pyogenic infection the following formula can be prescribed

SUBSTANCE	AMOUNT
Menthol	0.5 gm
Phenol	1.0 gm
Ichthammol	7.5 gm
Zinc oxide	30.0 gm
Olive oil	100.0 cc
Lime water (as needed) to make a solution of	250.0 cc

In prescribing liniments other than those of the *National Formulary*, it is well to advise the pharmacist to use an electric mixer. Wetting agents, such as sodium lauryl sulfate, are valuable additions to liniments. Their effectiveness is based on their power to reduce surface tension between the solid and the solvent, thus permitting penetration and dispersion of the solid. The following formula is smooth and efficient

SUBSTANCE	AMOUNT
Zinc oxide	15.0 gm
Calamine	15.0 gm
Olive oil	60.0 cc
Sodium lauryl sulfate	5.0 gm
Phenol	0.5 gm
Water (as needed) to make a solution of	250.0 cc

In persistent infiltrated extensive areas in which there is no evidence of infection, tar is useful, but it should be employed sparingly and only in the late stages. Liniments are of most benefit in an extensive eruption due to sensitization when the vesiculation has ceased, the crusts have become detached and the skin is red, dry and pruritic — that is, after the acute stage has subsided

The majority of occupational dermatoses should be cured by the use of wet dressings, lotions and finally, pastes and emulsions. Creams and ointments cause many of the complications of the treatment of occupational dermatoses. Ointments, especially, having no evaporating properties and being comparatively free from water, cause irritation and congestion when used in the initial stages. They may be employed in the subacute stage or in persistent eruptions. Neocalamine and Calamine Ointment (*National Formulary VII*) are excellent preparations. In fact, if physicians would prescribe more ointments of the *National Formulary*, they would have more expertly compounded prescriptions and less sensitization. When ointments contain drugs such as phenol, mercury, resorcin, Furacin and benzocain, the sulfonamides and penicillin, there is danger of absorption or sensitization. If there is no infection, there is no indication for the use. If secondary infection occurs, these drugs may be employed with caution and rarely for over one week, for by that time the infection should be believed

Ordinarily, an occupational dermatosis needs no internal therapy. When there is secondary infection, however, a sulfonamide or penicillin may be indicated. I prefer 50,000 units of penicillin in physiologic saline solution intramuscularly every three hours, it should be given no longer than five days because that period is usually sufficient and sensitization is avoided. A dosage of 300,000 units of penicillin in wax and peanut oil daily is also useful but the possibility of sensitization is increased by allergenic properties of the peanut oil. Benadryl and Pyribenzamine should be given during the period of injection. They have been helpful in controlling the spread and itching in the sensitization type of occupational dermatoses. If the patient is working, Benadryl should not be given because of its tendency to cause drowsiness. I prefer Pyribenzamine, which seemed to be of value in a few cases of industrial dermatitis. Autohemotherapy, alone or combined with previous intravenous injections of calcium gluconate, apparently helps when there is considerable edema or rapid extension of the eruption

Some readers may criticize this array of formulas. Everyone knows that a normal skin may prefer one soap to another, usually owing to the difference in the reaction or to the amount of free alkali present, or a woman may try a dozen face powders before she finds one suitable to her skin. How much more important is topical application prescribed for the injured or traumatized skin. Frequently, a patient states that irritation or no relief resulted after the use of calamine lotion, but when she is persuaded to use the same lotion modified by the addition of boric acid, talc or starch or coal-tar solution, an immediately soothing response is obtained. A resourceful and successful therapist must have many topical applications at his com-

similar. The capsules were smooth. The parenchyma was pale and bulging with edema. The renal pelvis, as well as the remainder of the genitourinary system, were not abnormal. Atherosclerosis in addition to marked interstitial edema and an occasional small hemorrhage there was precipitated protein throughout all portions of each nephron (Fig. 3). The outstanding abnormalities were observed in the distal convoluted and collecting tubules, many of which showed necrosis and varying stages of regeneration. The latter process predominated. Many of these tubules contained

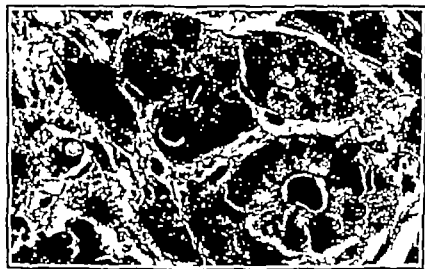


FIGURE 2 Intranuclear Inclusion Body in Liver Cell

intraluminal masses of red brown material — so-called pigment casts. In places these were surrounded by polymorphonuclear and histiocytic phagocytes. A few tubular cells contained intracytoplasmic droplets of yellow-green material resembling bile pigment. No inclusion bodies were found.

There was some edema of the lungs and brain but no other significant abnormality.

The findings in the kidneys were identical with those described by Lucke<sup>4</sup> as characteristic of "lower nephron nephrosis," a clinical and pathological syndrome that may complicate a variety of medical and surgical conditions. The syndrome frequently follows transfusion incompatibilities,<sup>5</sup> but in the case presented above, manifestations of renal damage preceded transfusion. The syndrome may also follow intravascular hemolysis in malaria,<sup>10</sup> severe burns<sup>11</sup> and sulfonamide-sensitive states.<sup>1</sup> The patient described above did not have malaria, nor was he burned. Other evidence of sulfonamide sensitivity was lacking. Necrosis of the lower nephron and the presence of pigment casts have also been described in a variety of liver diseases. Under such circumstances the renal pathology is usually referred to as cholemic or "bile" nephrosis. In the present case it seems likely that the renal lesions were secondary to the severe liver damage.

In that event the findings in the liver are not pathognomonic of any specific condition. They are, however, inconsistent with the lesions produced by sulfonamide sensitivity.<sup>12</sup> Except for the occasional case in which sensitivity develops, evidence of a hepatotoxic action on the part of any of the sulfonamides is highly questionable, a point empha-

sized in two recent reviews of the subject.<sup>13, 14</sup> That the sulfonamides play no part in the production of post-hyperthermia hepatitis was demonstrated by Wallace and Bushby,<sup>15</sup> who showed that the incidence of jaundice was no greater among patients simultaneously receiving sulfonamides than among those not receiving them.

The possibility that the hepatitis of hyperthermia is of virus origin has occurred to several observers. Such a concept presupposes the presence of a hepatotoxic agent latent in the body and in some way activated by the treatment. Fever therapy was repeated in 2 of MacDonald's<sup>3</sup> jaundiced patients and in 1 of our own. In no case did clinical jaundice reappear after the second treatment.

The virus of herpes simplex is harbored by many people, and when the proper stimulus — including heat — is forthcoming, clinical herpes appears. Herpes labialis has always been a common complication of artificial fever therapy. It occurred in 66 per cent of our own cases. Although the intranuclear inclusions found in the liver in the case presented above are indistinguishable from those found in herpes simplex infections, this does not imply a herpetic or even a virus etiology for the



FIGURE 3 Section of a Kidney Showing Damage to Tubular Epithelium and Pigment Casts

hepatitis. Inclusion bodies of one sort or another have been described and produced in a great variety of nonvirus conditions. Inclusions indistinguishable from those of yellow fever, for example, have been observed in liver cells of burned patients treated with tannic acid.<sup>16</sup> Furthermore, the virus of herpes is not known to infect the liver of man or animal.

The patient, like all military personnel in the theater, had previously received attenuated yellow-fever-virus vaccine. At the time the fever treatments were being given, hepatitis was fairly prevalent among the troops. Whether "epidemic" and "serum" hepatitis are in reality the same disease has not yet been established. It has been amply demonstrated, however, that the serums of certain



persons at times harbor a hepatotoxic virus. Whether it can be activated by fever is at the moment unknown. Morphologically, except for the presence of inclusion bodies, the liver in the case discussed above bears many similarities to the pathology of infectious hepatitis described by Lucké<sup>17</sup> and many others. From a clinical point of view, however, the hepatitis that follows fever therapy is as a rule less severe and of considerably shorter duration than the infectious hepatitis.

A more probable etiology for this form of hepatitis is to be found in high body temperatures per se. Although the critical temperature above which liver cells become irreversibly damaged is unknown and probably varies to a certain extent with the state of nutrition of the individual cells, there is evidence that this point is not far above those frequently encountered. King et al.<sup>2</sup> showed that the incidence of jaundice among patients receiving fever therapy was higher in a group whose temperatures were maintained at 106.6°F than in a group held at 106.0. More significantly, they noted that jaundice was particularly likely to occur if the temperature were allowed to rise for even brief periods above the former figure. Evidence also exists that the majority of patients receiving intensive fever therapy suffer some degree of liver damage, even though clinical jaundice fails to appear. The same authors showed that in a group of 40 consecutive cases a subclinical rise in serum bilirubin occurred in 75 per cent. Hippuric acid tests performed before treatment and repeated three days later showed a significant reduction in liver function in 12 cases. Wilson and Doan<sup>18</sup> studied a similar group of patients and found a post-therapeutic rise in bilirubin and an increased retention of brom-sulfalein in each case, the degree and duration of fever were not recorded.

Although observations on animals subjected to experimental hyperpyrexia include no clinical or pathological effects exactly comparable to post-hypertherm hepatitis in man, changes in the liver have frequently been described. Hartman and Major<sup>19</sup> placed dogs in a Kettering hypertherm cabinet and maintained their rectal temperatures between 107 and 110°F (41.7 and 43.3°C) for five to seven hours. The animals died or were sacrificed at intervals from one to seventy-two hours later. The predominant lesions were those of congestion and hemorrhage, but many livers showed extensive midzonal necrosis. Hall and Wakefield<sup>20</sup> maintained dogs at comparable temperatures by similar means. Lesions in the liver were limited to cloudy swelling, probably because the animals were examined too soon after exposure for more significant morphologic changes to have developed. Other investigators have raised the temperatures of animals by less pertinent means. Jacobsen and Hosoi,<sup>21</sup> using high-frequency currents, maintained dogs for periods up to twelve hours with rectal temperatures

of 108 to 111°F (42.2 to 44.0°C). Most of the dogs died promptly, but some of the survivors showed focal necroses in the liver.

Rawlinson and Kellaway<sup>22</sup> perfused cat livers with hot saline solutions and determined in the perfusate the concentrations of several cellular constituents. Their results indicate that liver cells are severely damaged by temperatures as low as 104°F (40°C) when maintained for six hours. Although the conditions of perfusion produced cellular damage, that which occurred at high temperatures was significantly greater than could be accounted for by a simple exponential increase in the rate of processes operating at body temperature.

Opportunity for studying the morphologic effects of high temperatures on the human liver does not occur often because hyperpyrexia usually brings death within a few hours or the patient survives. In prompt deaths signs of cerebral damage dominate the clinical and pathological picture. The liver may show "cloudy swelling." Occasionally, however, the survival period is adequate for clinical signs of liver failure and for morphologic manifestations of necrosis to develop. Wilbur and Stevens<sup>6</sup> described a patient who lived for three days after a sunstroke during which the temperature had reached 110°F (43.3°C). Jaundice was present, and there was definite evidence of necrosis in the liver. Malamud, Haymaker and Custer<sup>23</sup> recently studied the pathology in 125 fatal cases of heatstroke among American troops. They found frank necrosis of the liver in only 12 cases, but all these occurred in patients who had survived for more than thirty hours, whereas the majority had died in less than twenty-four hours. Jaundice appeared clinically in some of the former group.

It is a common biologic observation that unicellular organisms differ widely in their sensitivity to heat, the critical temperature being, within limits, specific for the species. Among multicellular organisms certain highly differentiated cells are more sensitive to heat than less differentiated ones. In man there is evidence that hepatic cells, along with certain cells of the central nervous system, are among the first to be damaged by high temperatures. Although the part played by oxygen deficiency may be an intimate one, destruction of essential enzyme systems appears a more probable mechanism.

SUMMARY

Hepatitis, with or without jaundice, frequently complicates artificial fever therapy. Liver damage also occurs after other forms of hyperpyrexia.

The pathological findings in a fatal case of post-hypertherm hepatitis are presented. The liver showed extensive necrosis followed by regeneration.

Available evidence indicates that liver cells, in addition to certain cells of the nervous system, are particularly susceptible to damage by high fever.

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## SYPHILITIC PRIMARY OPTIC ATROPHY\*

## A Review of 54 Cases

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BOSTON

A FEW years ago the outlook regarding vision for patients with syphilitic primary optic atrophy was generally considered extremely poor, regardless of the type of therapy used. This attitude tends to persist in spite of the gratifying reports by Moore et al.<sup>1</sup> and others<sup>2, 3</sup> of unusually successful results with malaria treatment. One of the reasons for pessimism is that there is too often an excessive delay in starting treatment and that, as a result, optic atrophy may progress to blindness before adequate treatment is instituted. This delay often appears to be due to failure to make the proper diagnosis, lack of appreciation of the potential rapidity of progress of the disease or confusion regarding what constitutes adequate or proper therapy.

In view of these considerations we have undertaken to report an analysis of our cases of syphilitic primary optic atrophy.

## MATERIAL

A series of 54 patients with syphilitic primary optic atrophy admitted to the Boston Psychopathic Hospital during the years 1921 to 1944 formed the basis of the investigation. The case records were reviewed and analyzed from the point of view of history, clinical findings and response of vision to treatment.

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The ages ranged from nineteen to sixty-two years. The age-distribution curve was essentially the same as that for patients with neurosyphilis in general, the maximum number of cases occurring between the ages of forty and fifty.

Of the 54 patients, 51 were males and 3 were females. There were only 2 Negroes in the series.

The duration from the occurrence of the primary syphilitic lesion to the onset of the visual loss (as judged by data available in only 20 cases) varied from ten to thirty-three years, with an average of twenty years.

## FIRST MANIFESTATIONS OF NEUROSYPHILIS

The first clinical manifestations of neurosyphilis in cases that later developed optic atrophy were as follows:

SYMPTOM	No. of Cases
Gradual loss of vision	34
Lightning pains	3
Personality change	3
Difficulty in concentration or memory	3
Gastric crises	2
Pain in eyes	2
Diplopia	1
Proctitis	1
Numbness on right side of face	1
Dysarthria	1
Urinary incontinence	1
Aphasia	1
Total	54

It is interesting that in 34 cases (63 per cent) the first manifestation was gradual loss of vision. It

is therefore apparent that every patient with the complaint of gradual loss of vision should have adequate investigation for central-nervous-system syphilis, even when other signs are absent

SEROLOGIC FINDINGS

In all but 1 case there was a report of the admission blood Wassermann or Hinton test, or both. In 39 cases blood Hinton tests were positive in 38 and doubtful in 1. In 19 cases blood Wassermann tests were positive in 13, doubtful in 2 and negative in 4. From these data it is apparent that a negative blood Hinton or Wassermann test is rare in untreated or inadequately treated cases of syphilitic primary optic atrophy.

PUPILLARY ABNORMALITIES

Of 51 cases in which the pupillary findings were recorded on admission, 49 showed pupillary abnormalities characteristic of neurosyphilis. Thirty-six patients were recorded as having Argyll-Robertson pupils, and 13 as having irregularity, inequality of the size of the pupils or absent light reaction.

DIAGNOSIS ON ADMISSION

After careful study of the case records, the following diagnoses were made: syphilitic primary optic atrophy alone, 15 cases; syphilitic primary optic

though visual acuity was markedly diminished. These findings are in contrast to those in trypan-blue optic atrophy, in which marked constriction of the visual fields often occurs and is usually accompanied by only slight loss of central vision.

DEVELOPMENT OF BLINDNESS\*

In 43 cases in which data were available, the onset of visual loss was bilateral in 11 and unilateral in 32. Of the latter group, 16 cases began with involvement of the right eye and 16 with involvement of the left eye. Cases with unilateral onset, if untreated, usually developed involvement of the second eye within a few months. In untreated cases, however, optic atrophy occasionally remained unilateral for longer periods, the maximum duration being three years.

Untreated cases showed widely differing rates of progression. In the most rapidly progressive case complete blindness developed bilaterally within twenty-two days. The patient with the slowest progress, after seven years without treatment, had visual acuity of 10/100 in one eye and blindness in the other. One of the notable trends was the rather frequent development of blindness in both eyes within a twelve-month period, emphasizing the need for intensive early treatment.

TREATMENT BEFORE ONSET

In this series treatment prior to the development of optic atrophy was inadequate, permitting the hypothesis that visual involvement might have been prevented had more active measures been used. Only 15 patients (28 per cent) received any treatment prior to the development of optic atrophy. In these cases, chemotherapy alone was employed, consisting usually of only a few arsenical and bismuth injections. No patient in the series received fever treatment before the onset of optic atrophy.

Ten patients who had been fortunate enough to receive chemotherapy were given this treatment two to twenty years before the development of any evidence of optic atrophy. Five patients, however, developed the first signs of optic atrophy while receiving a course of routine antisyphilitic treatment. Therefore, syphilitic optic atrophy may begin and progress in some persons even though active chemotherapeutic measures are being used. In other words, chemotherapy is no guarantee against the development of optic atrophy.

EFFECT OF TREATMENT

Of 43 patients who were not totally blind when treatment was started, 27 were followed for two years or longer after treatment had been instituted. The average duration of follow-up study in these cases was seven years.

Figure 1 shows the superiority of fever therapy as compared to chemotherapy in these cases. Of

TABLE 1 Degree of Tabetic Involvement in Cases with Tabetic Features

INVOLVEMENT	NO OF CASES	NO OF CASES WITH LIGHTNING PAINS	NO OF CASES WITH TABETIC BLADDER	NO OF CASES WITH HISTORY OF GASTRIC CRISES
No ataxia: absence of tendon reflexes in lower extremities	15	4	2	3
Slight to moderate ataxia or positive Romberg sign	10	6	1	0
Marked ataxia	0	—	—	—

atrophy with tabes, 20 cases; syphilitic primary optic atrophy with general paresis, 14 cases; and syphilitic primary optic atrophy with taboparesis, 5 cases.

In 19 cases there was a paretic element, whereas in 25 there was a tabetic element. Our experience that optic atrophy is found much more frequently in association with tabes than with general paresis coincides with the reports of others.<sup>1</sup> Optic atrophy occurs more commonly, however, in association with general paresis than may be generally appreciated.

An analysis of the degree of tabetic involvement in the 25 cases with tabetic features is presented in Table 1. It was observed that the tabetic picture was essentially one of a mild degree, none of the cases showing marked ataxia.

VISUAL FIELDS

In general, the visual fields showed irregular constriction, which was usually of moderate degree even

\*In this study an eye was considered blind if the visual acuity was 1/200 or less.

the 11 patients treated only with chemotherapy,\* 6 (55 per cent) were blind on follow-up study of two years or longer. Of the 16 patients treated with fever therapy in addition to chemotherapy, only 2 (13 per cent) were blind on follow-up examination two years or more after treatment. In these 16 cases, fever therapy was usually followed by chemotherapy for one year or more. In 4 of the 16 cases, fever was artificially induced. The remaining 12 patients received malaria treatments, the number of chills varying from five to seventeen. The series of cases is too small to determine whether treatment with malaria was superior to treatment with artificial fever. It is interesting, however, that none of the 4 patients treated with artificial fever were found to be blind on follow-up study.

In general, the cases treated with chemotherapy had been of a less rapidly progressive variety prior to treatment than those chosen for fever therapy. It is also worth noting that in all 5 patients whose visual loss was arrested by means of chemotherapy alone the optic atrophy was essentially unilateral, on follow-up study all were found to be blind in one eye but to have little or no visual loss in the other. Moore<sup>1</sup> has stressed the fact that patients in whom the atrophic process is still unilateral respond best to treatment. These 6 cases, therefore, comprised a selected group of patients who were most suitable for treatment and in whom chemotherapy alone was apparently sufficient to prevent blindness in the eye showing little or no involvement. One is not justified, however, in recommending chemotherapy alone for such cases because in similar cases treated with chemotherapy follow-up study revealed complete blindness in both eyes.

In the entire series there were only 2 cases in which vision improved after treatment, and in both, the treatment had consisted of intensive malaria therapy followed by chemotherapy. In 1 case, immediately prior to the onset of treatment, the patient was blind in the right eye and had 20/100 vision in the left, four years later visual acuity was found to be 20/200 in the right eye and 20/30 in the left. In the other case, immediately before treatment, the patient was blind in the left eye and had 20/40 vision in the right, but three months later visual acuity was found to be 20/200 in the left eye and 20/20 in the right. It is not to be expected, however, that therapy will improve vision but that, with good fortune, vision will not be further impaired.

#### CEREBROSPINAL-FLUID FINDINGS

The cerebrospinal-fluid findings were classified according to severity as Group I, II or III (the last being the strongest and equivalent to the so-called "paretic formula"), in accordance with the classification of Moore.<sup>1</sup> Analysis of the first cerebrospinal-fluid findings recorded after the onset of syphilitic primary optic atrophy revealed that 41

patients (76 per cent) had Group III fluids whereas 13 had Group II fluids. Of the latter, 11 patients (85 per cent) had received treatment during the interval between the onset of the optic atrophy and the examination of the fluid. Of the 41 patients with Group III fluids, however, only 19 (46 per cent) had received treatment during the interval between the onset of the optic atrophy and examination of the fluid. These findings indicate that, in general, syphilitic primary optic atrophy is accompanied by

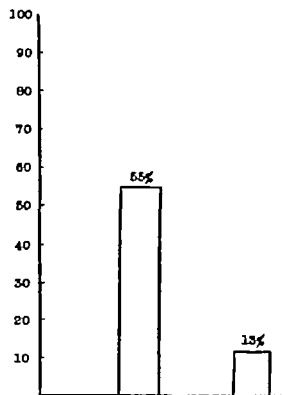


FIGURE 1. Results of Treatment of Syphilitic Primary Optic Atrophy by Means of Chemotherapy as Compared to Fever Therapy Combined with Chemotherapy, on Follow-up Study of Two Years or Longer.

strongly positive cerebrospinal-fluid findings unless antisyphilitic treatment has been started.

A further study was made of the cerebrospinal fluid in cases in which, as a result of treatment, optic atrophy had become definitely arrested for two years or longer (from two to fifteen years). There were 11 such cases, in 10 of which the cerebrospinal fluid had been examined during the six months following arrest of the optic atrophy. Only 1 of these patients had a Group III fluid, 3 a Group II fluid, 5 a Group I fluid and 1 a normal fluid. In the 9 cases with positive cerebrospinal-fluid findings the fluids later became negative with continued treatment (from nine months to about seven years). There was only 1 case in which visual loss was progressive after the cerebrospinal fluid had become negative. Since this patient was a diabetic, aged sixty years, the question whether the progression of visual loss was due to diabetic retinopathy rather than syphilitic primary optic atrophy remained unanswered.

The above data indicate that, in general, syphilitic primary optic atrophy becomes arrested before the cerebrospinal fluid becomes normal and that, when

\*Four patients received intrathecal or intracisternal treatment in addition to routine chemotherapy.

the optic atrophy becomes arrested, the cerebrospinal-fluid findings usually fall in Group I or II

### DISCUSSION

One of the most striking findings was the high incidence of Group III cerebrospinal fluids (paretic formula) in cases of syphilitic primary optic atrophy, even though many of the patients had received some treatment before examination. These findings support the histologic studies of Bruetsch,<sup>4</sup> who states that "the pathologic basis of syphilitic optic atrophy is more like the process of dementia paralytica than of tabes," and remarks further that his findings uphold the anatomic studies of Leri,<sup>5</sup> Stargardt<sup>6</sup> and Richter<sup>7</sup> that the primary lesion in syphilitic atrophy of the optic nerve is a peripheral and interstitial neuritis, which is followed by a slow, secondary degeneration of the nerve fibers. Many writers on this subject have been so fascinated by the term tabetic optic atrophy that they have overlooked this important conclusion of the early workers or have become confused by the many different opinions expressed on the pathogenesis of optic atrophy.

This point of view is in contrast to that previously expressed by Moore and Woods<sup>8</sup> that the pathogenesis of syphilitic primary optic atrophy, which is often associated with tabes dorsalis, is identical with that of tabes dorsalis itself.

Indirect evidence in support of the conclusions of Bruetsch is found in the extensive perimetric studies of Sloan and Woods,<sup>9</sup> who observed that the lesion responsible for syphilitic atrophy of the optic nerve and visual-field defects lies in the optic nerves rather than in the chiasm or posterior to it and is probably a peripheral and interstitial neuritis associated with secondary degeneration of the nerve fibers.

In view of the strongly positive cerebrospinal-fluid findings in syphilitic primary optic atrophy one might anticipate that these patients would require at least as intensive treatment as patients with general paresis. This appears to be true, and since blindness may develop rapidly, it is our opinion that all these patients should receive the most intensive treatment available as early as possible in the course of the disease, in the hope of preventing further damage to diseased nerves and thereby of preserving useful vision. In a review of our cases it became apparent that several cases had progressed to complete blindness without treatment and that in many others intensive treatment had been delayed or lacking.

Our favorable results with malaria therapy support the findings of Moore,<sup>1</sup> who reported that of 32 patients receiving malaria therapy, only 14 per cent were blind at the end of two years.

Unfortunately, we had too few patients treated with artificial fever to be able to evaluate its effectiveness adequately. In the 4 cases treated, how-

ever, the results were satisfactory. When these cases are added to those of Menagh,<sup>10</sup> who obtained a satisfactory outcome in 4 of 6 cases so treated, Culler and Simpson,<sup>11</sup> who obtained satisfactory results in 13 of 16 cases, and Neymann and Osborne,<sup>12</sup> who obtained a satisfactory response in 4 of 6 cases, one is left with the impression that artificial fever is definitely effective in syphilitic primary optic atrophy.

### SUMMARY

In 54 patients with syphilitic primary optic atrophy, seen at the Boston Psychopathic Hospital between 1921 and 1944, the first manifestation of neurosyphilis was usually gradual loss of vision.

Although syphilitic primary optic atrophy occurs most frequently in association with tabes, as a rule the tabetic features are mild.

Some abnormality of the pupils characteristic of neurosyphilis is almost always present.

A negative blood Wassermann or Hinton test is rare in untreated or inadequately treated cases.

Syphilitic primary optic atrophy is, in general, accompanied by a strongly abnormal cerebrospinal fluid (Group III) characteristic of the paretic formula. This finding is consistent with the studies of Bruetsch, in which the pathologic basis of this disorder was found to be more like the process of general paresis than that of tabes.

Syphilitic primary optic atrophy may respond well to fever therapy provided that treatment is started before useful vision is lost. Of 16 patients treated with artificial fever only 2 (13 per cent) were found to be blind on follow-up study of two years or longer. Although the available data are insufficient to determine whether artificial fever is as effective as malaria therapy, the former is definitely an important addition to the therapeutic armamentarium.

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## INHIBITION OF CUTANEOUS PAIN RESPONSES BY THE LOCAL APPLICATION OF COLD\*

## A Simple Method of Reducing the Pain of Hypodermic Injections

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THE increased use of antibiotic therapy as well as other medications and fluids administered by hypodermic injection has raised the question of the effectiveness and practicality of employing cold to relieve the pain of the repeated and often terrifying encounters with the needle experienced particularly by sick children. Inquiry revealed that hundreds of intramuscular and subcutaneous injections alone are performed every day at the Children's Hospital. Frequently, the mental and physical anguish associated with the numerous injections given to a critically ill patient is not inconsiderable.

It seemed desirable to determine first of all the physiologic relation between the temperature of the skin and the discharge of impulses from cutaneous pain receptors. That nerve conduction may be temporarily interrupted by temperatures that never reach the freezing point is well known. This has been demonstrated clinically by the effectiveness of refrigeration anesthesia in surgery of the extremities. It has also been measured in experimental animals. Denny-Brown and his co-workers<sup>1</sup> cooled the exposed sciatic nerve of cats with circulating brine. They found that when the temperature of the brine was 2°C or higher and the temperature within the nerve itself 8 to 11.6°C for as long as two hours, there was temporary interruption of function with no evidence of any permanent damage to the nerve. Gasser<sup>2</sup> studied the effect of temperature changes on nerve conduction in the frog. He found that cooling a nerve caused its action potential to decrease in a characteristic way. On cooling from 30 to 20°C, the action potential fell off slowly. The rate of fall then progressively increased, and somewhere in the neighborhood of 10°C the decline became rapid, with failure to respond altogether around 5°C. If cooling was discontinued at that temperature, the process was still reversible, since complete recovery occurred when the nerve was rewarmed.

Few clinical observations have been made on the effect of cooling on cutaneous sensation, although the numbing effects of cold, particularly that applied to the extremities, is a daily observation during ordinary winter exposure. Gammon and Starr,<sup>3</sup> in the course of studies on pain relief by counter-irritation, found that cold was most effective when

applied to the skin at a temperature of 4 to 10°C. They observed cold to be more effective in relieving pain caused by irritant surface ointments than electricity, heat, vibration or air-jet stimulation. They accounted for the principal effect of cold in relieving pain on the basis of a decreased peripheral sensory discharge due to lowering of the temperature of the pain endings.

## EXPERIMENTAL OBSERVATIONS

Experiments were undertaken to determine the feasibility of quick-cooling a small area of skin to a degree that would permit painless insertion of a needle. The area of skin that need be cooled for any one injection is small, it need remain cooled to an effective degree only long enough to carry out introduction of the needle—fifteen to thirty seconds. A small portable instrument capable of quickly cooling the skin to a degree sufficient to inhibit the cutaneous pain receptors temporarily but not producing pain in itself or any irreversible alterations in the skin or cutaneous receptors involved seemed desirable. Such an instrument, to be of practical value, demanded simplicity and suitability for use by nurses without danger of local skin damage.

After preliminary experiments with carbon dioxide snow in various types of containers, a much simpler instrument was constructed and has proved satisfactory for certain fundamental observations and for the carrying out of numerous clinical trials. A brass cylinder, 5 cm in diameter and 22.5 cm long, closed at one end, was selected. A smaller brass cylinder, 1 cm in diameter and 1 cm in length, was soldered on to the middle of the closed end of the larger cylinder. This small cylinder was filled with solder (20 per cent lead and 80 per cent tin), a rapid conductor of heat. The large cylinder was wrapped with felt 0.5 cm in thickness. It was filled with cracked ice to which was added anhydrous calcium chloride. The open end of the cylinder was occluded by a tightly fitting rubber cork. The opposite, or contact end, was covered by a hollowed-out, closely fitting rubber cap. This gave a compact insulated instrument with a cooled round metallic contact surface 1 cm in diameter (Fig. 1). It was found that with cracked ice alone in the brass cylinder, the temperature of the contact surface, as determined by an iron-constantan thermocouple (L & N Potentiometer), was about 7.5 to 9.5°C. By the addition of varying amounts of calcium

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chloride to the cracked ice the temperature of the contact surface could be reduced as low as  $-4^{\circ}\text{C}$ . If the cylinder was kept completely insulated — that is, with the rubber cap over the contact surface except when in use — the temperature of the contact remained at approximately the same level for several hours. If the instrument remained in a refrigerator when not in use, the temperature of the contact could be kept at desired levels for longer periods.

Numerous observations were first made on healthy subjects, to determine the effectiveness of this cooling metallic contact in reducing the skin tem-

perature and index finger so as to exert counterpressure, there was no sensation when the needle was inserted.

Experiments were performed to determine the optimum temperature of the metal contact. It was found that a contact temperature of  $4$  to  $6^{\circ}\text{C}$  proved most satisfactory. If the temperature was below  $4^{\circ}\text{C}$ , application of the contact became uncomfortable and, in areas of thin skin, such as the volar aspect of the forearm, definitely painful, owing to a local burning and aching sensation. If the temperature was above  $7^{\circ}\text{C}$ , the skin was not cooled to the critical level found essential for tem-

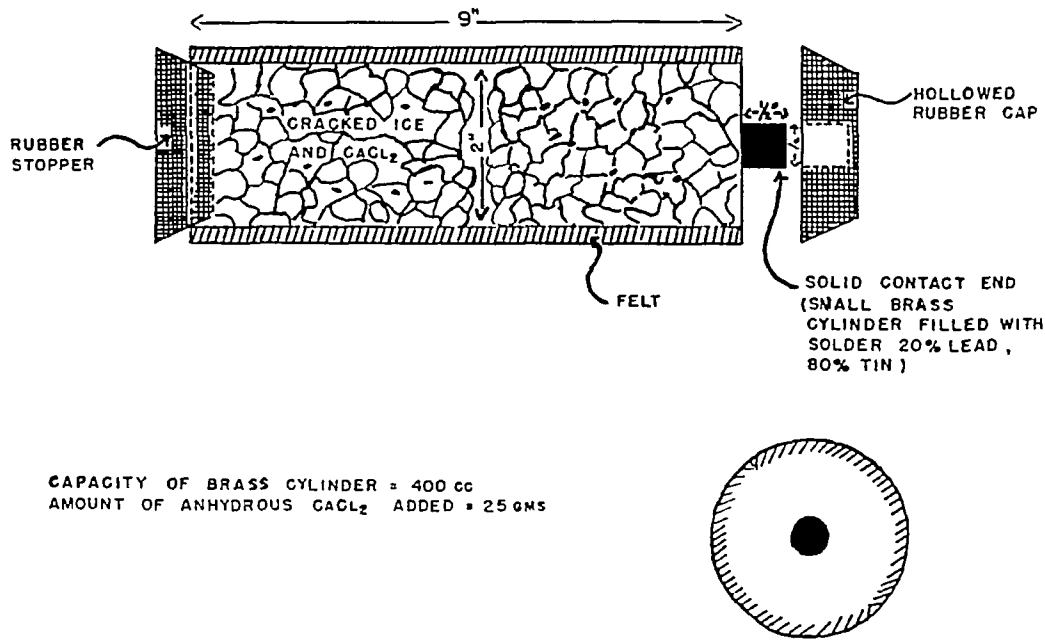


FIGURE 1 Instrument for the Local Application of Cold

perature. These were made at room temperatures of  $21$  to  $28^{\circ}\text{C}$ . Skin temperatures were recorded from a potentiometer with the use of an iron-constantan thermocouple. Tests were made on many skin areas, notably those generally used for hypodermic injections: the lateral aspect of the upper arm, the lateral and dorsal aspects of the thigh, the lateral aspect of the buttock and the volar and dorsal surfaces of the forearm. It was soon determined that when the skin temperature was reduced to a point between  $11$  and  $14^{\circ}\text{C}$ , preferably below  $13^{\circ}\text{C}$  (normal skin temperature equals  $31$  to  $34^{\circ}\text{C}$ ), an ordinary No. 23 to 19 hypodermic needle could be introduced through the cooled skin without pain. This proved to be consistent in different subjects, at different testing periods and on different areas of skin. Pressure was perceived by the subject as the needle was pushed through the cooled skin, but no pain. If the cooled skin was elevated and pinched between the operator's

porary inhibition of cutaneous pain receptors. The ideal temperature, therefore, was  $\pm 5^{\circ}\text{C}$ . It was found that  $25$  gm of anhydrous calcium chloride added to the  $400$  cc of cracked ice in the instrument used consistently produced this temperature of the metal contact. By determination of skin temperatures in various areas of the body after the contact had been applied at temperatures between  $4.4$  and  $5.5^{\circ}\text{C}$  for varying periods, it was observed that forty-five to sixty seconds' cooling was adequate to reduce the skin temperature to the critical level for anesthesia (Fig. 2). The temperature remained within this range for thirty to sixty seconds. After that period, sensation gradually returned as the skin became warmer. The application of a tourniquet to the extremity proximal to the point of cooling did not affect the rate or degree of reduction of skin temperature by this method.

Cooling the surface of the skin did not lessen the discomfort of intradermal injections of fluid. After cooling of the skin to 11 to 13°C an intradermal needle could be inserted entirely without pain, but subsequent injection of novocain or physiologic saline solution produced a momentary, intensely painful sensation, presumably by providing a different type of stimulus (distention of the skin),

also be pain on actual injection into the substance of the muscle, depending on the nature and amount of the material injected.

It can also be used satisfactorily in routine venipunctures. The needle is inserted painlessly through a cooled area of skin immediately over or adjacent to a prominent superficial vein. Once through the skin there is little or no pain connected with seeking

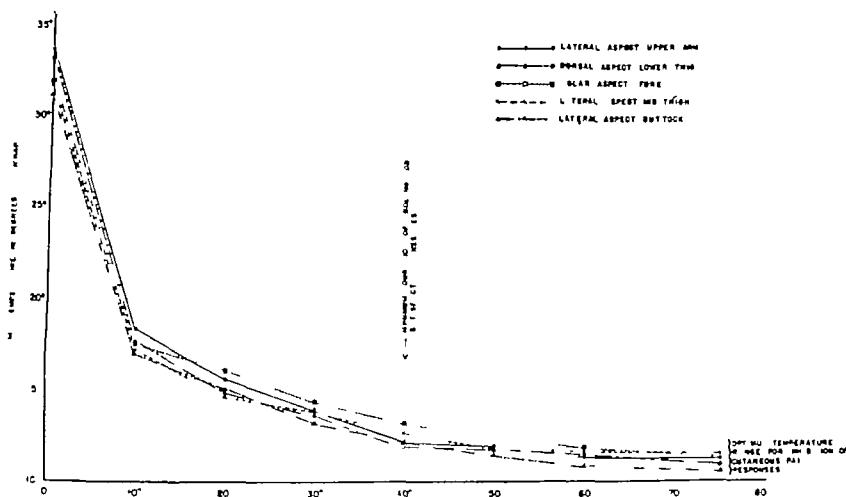


FIGURE 2 Duration of Cooling with Metal Contact at 4.4 to 5.4°C

The time is expressed in seconds and each point charted represents the average of three readings

which stimulated cutaneous endings not affected by the cooling. The method, therefore, is unsatisfactory for preliminary anesthesia of an area of skin subsequently to be anesthetized for prolonged insertion of a needle — as in lumbar puncture.

#### CLINICAL APPLICATION

The application of this principle of local quick-cooling of the skin is widest naturally for subcutaneous injections: these can be done entirely without pain by the application of a metal contact whose temperature is  $\pm 5^{\circ}\text{C}$  to an area of skin for forty-five to sixty seconds, especially if the pressure of insertion of the needle is eliminated by counter-pressure on the adjacent skin. A metal contact at  $5^{\circ}\text{C}$  feels cold but is not uncomfortable in that length of time except over areas of extremely thin skin. On the lateral aspect of the upper arm, the thigh and the buttock it is not at all unpleasant. The method is extremely effective for intramuscular injections, although occasionally slight twinges of pain are felt as the fascia is pierced, and there may

the lumen of the vein with the point of the needle. If the procedure takes longer than sixty seconds owing to the operator's inability to insert the needle into the vein promptly, manipulations of the needle at the skin surface will again be painful.

This device has been used as follows on numerous children, as well as on adult patients. If old enough, the patient is told about the purpose of the cooling metal disk. Since most patients have had previous painful injections, they are receptive to its use. The skin area to be injected is prepared as usual by being wiped clean with an alcohol or Zephiran sponge. The rubber cap is removed from the cold contact surface, and the latter is also wiped with an alcohol or Zephiran sponge. The contact surface is held against the cleaned skin for forty-five to sixty seconds. The cooled skin is then gently elevated by squeezing together of the adjacent skin on either side, and injection performed through the center of the cooled area within thirty seconds. If patients looked away they were frequently entirely unable to tell the moment of insertion of the needle.



This method of local quick-cooling has been used satisfactorily for all types of subcutaneous medications, intramuscular chemotherapy, venipuncture for removal of blood and administration of drugs and for the insertion of subcutaneous clyses

### SUMMARY

When the skin temperature is reduced to 11 to 13°C by external application of cold to a small area, pain responses to cutaneous stimuli in this area are inhibited

A smooth metal disk at a temperature of  $\pm 5^{\circ}\text{C}$  held against the skin for forty-five to sixty seconds will reduce the skin temperature to 11 to 13°C for periods of thirty to sixty seconds

During that interval hypodermic needles can be inserted through the cooled skin entirely without pain, and with no sensation if the pressure of intro-

duction of the needle is equalized by counter-pressure on the adjacent skin

Reducing the skin temperature locally to this level is without danger, produces no irreversible changes and is not uncomfortable

The method has been found useful, particularly in children, for the carrying out of painless hypodermic injections and all forms of parenteral therapy

Any simple device, such as the one described above, that will provide a small metallic surface at a temperature consistently in the neighborhood of  $5^{\circ}\text{C}$  is suitable for practical use in office or hospital

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## MEDICAL PROGRESS

### PRACTICAL CONSIDERATIONS OF VENOUS PRESSURE\*

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CLINICAL interest in venous pressure has centered mainly on the alteration in its measurement in cases of heart disease<sup>1-7</sup> In this connection most of the literature on the subject is concerned with the utility of venous-pressure measurement in confirming the diagnosis and following the progress of congestive heart failure In addition, in the past few years the results of studies of venous pressure in its relation to the mechanism of heart failure have provoked a lively debate At the same time there have been noteworthy improvements in technic of measurement, as well as increasing awareness of the value of the test in the diagnosis and study of a number of other conditions, including pericarditis, thoracoplasty, shock and a variety of causes of localized venous obstruction

#### NORMAL PHYSIOLOGY

Before the clinical application of venous-pressure measurement is reviewed, it seems advisable to recall briefly the normal physiology of venous flow It is obvious at the start that the initial impetus to

flow of blood in the systemic veins is imparted by the propulsive action of the heart and arteries Of course, the capillary bed has a dampening effect on this action, so that the rate and volume of blood flow in the veins are more directly related to capillary pressure and flow It is essential to remember also that the veins adjust their capacity nicely to the volume of blood delivered by the capillaries, this adjustment depending on the same nervous and humoral influences that affect arteriolar and capillary tone At the other end of the venous circulation the heart has an important regulatory effect because of its ability normally to alter its output to suit wide variations in the volume of venous return On this account, stagnation of blood in the veins is prevented under conditions in which venous return is increased The flow of blood through the systemic veins receives another important propulsive force from the tone and intermittent contraction of the skeletal muscles This force moves blood only in the direction of the heart because of the arrangement of the venous valves Another factor that exerts a major influence in favor of venous return is the negative intrathoracic pressure This produces an expansion of the thin-walled intrathoracic veins so that venous blood tends to be sucked into the thorax Since the negative pressure in the thorax increases during inspiration and decreases during expiration, venous pressure fluctuates accordingly during the

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phases of respiration. Finally it must be mentioned that gravity influences venous flow and venous pressure. It is generally accepted that the right atrium represents the zero hydrostatic level for the blood in the veins — that is, the level at which gravity has no influence. In a vein located below this level, therefore, part of the venous pressure represents the weight of the column of blood interposed between the vein and the right atrium. It must be kept in mind that the effect of gravity is minimized by several mechanisms, including intramuscular pressure, muscle contraction, intra-abdominal tension and the system of venous valves.

Although there are numerous variables in the physiology of venous flow, some of them counterbalance in such a manner that venous pressure tends to be remarkably constant in normal subjects. In addition, the technic of measurement of venous pressure removes other variables. Before the measurement is made the patient is required to rest in bed for fifteen to thirty minutes. This prevents any alteration that might otherwise result from the effect of exertion.<sup>2</sup> During the test the patient is supine with the arm at an angle of 45° to the body and in such a position that the antecubital vein to be used is at or just below the level of the right atrium. This position of the arm eliminates any tendency to compression or torsion of the axillary or subclavian vein, which may result when the arm is closer to the side or more fully abducted.<sup>2</sup> Also, the fact that the vein selected for venipuncture is not above heart level prevents errors in measurement that might otherwise result from collapse of such superficial veins.<sup>2</sup> An effort is made to have the patient relax fully, so that muscle tension will not alter the results, and he is instructed to breathe easily and regularly to avoid the effects of alteration of the intrathoracic pressure. Apnea, sighing, straining, coughing, talking and other variations in the respiratory act prevent accurate evaluation of the venous pressure.<sup>4</sup> The supine position minimizes the effect of gravity, and in addition, the hydrostatic factor should be entirely eliminated by the use of a level for reference of the venous-pressure measurement at which hydrostatic pressure is zero.

A number of different zero levels have been used, and this has naturally led to some variation in the values reported for normal venous pressure.<sup>2,3</sup> Needless confusion has developed concerning the significance of this point. As a matter of fact, the selection of the zero level has made little practical difference in the results reported by various authors, except that the results must be evaluated individually and cannot be used interchangeably. The situation is analogous to that which obtains in connection with a laboratory test like the erythrocyte sedimentation rate. Various technics have been used, and the values found with one technic are not the same as those with another, although they are individually valid. There is much to recommend the zero level

selected by Lyons, Kennedy and Burwell at a point 10 cm from the skin of the patient's back when the supine position is utilized. This level closely approximates the plane of the right atrium and agrees remarkably well with results obtained by Holt<sup>5</sup> in a detailed study of the problem of eliminating the hydrostatic factor during venous-pressure measurement. Winsor and Burch<sup>6</sup> advocate the use of the "phlebostatic axis" to find the zero level for reference. They define the axis as a line resulting from the intersection of a frontal plane passing midway between the posterior surface of the body and the base of the xiphoid process, with a cross-sectional plane passing through the fourth intercostal space adjacent to the sternum. A horizontal plane passing through this axis is the phlebostatic level. The use of this level is recommended by its originators because it is supposed to give the same results regardless of the position of the patient. This appears to be true for normal persons but is far from true for patients with venous hypertension from any cause,<sup>3,4</sup> so that the arguments in favor of employing this reference level lose their force. With the patient supine the same reference level that is used for measurement of the venous pressure in the arm veins should be used for those in other veins, such as the femoral, for purposes of comparison.

#### TECHNIQS

The numerous variations in technic for measurement of venous blood pressure can be grouped in three categories, as follows: clinical inspection of superficial veins, the indirect method and the direct method.

##### *Clinical Inspection of Superficial Veins*

Inspection of suitable superficial veins is useful for estimation of the venous pressure only when the pressure is higher than normal, so that the veins are abnormally distended. Probably the most widely employed technic entails inspection of the external jugular veins.<sup>10,11</sup> When a patient is in a semi-sitting position, these veins normally are not filled above the plane of the manubrium. Distention of the veins above this level indicates that the venous pressure is abnormally high, at least in the superior-vena-cava system (Fig 1). This finding in a patient who also has hepatomegaly with or without edema of the lower part of the body permits the conclusion that there is a generalized elevation of the venous pressure above normal, such as that in congestive heart failure. At times in heart failure, abnormal distention of the jugular veins is not detected until the abdomen is firmly compressed, or this maneuver may increase the amount of distention (hepatojugular reflux). This point is discussed below in full.

Another technic for determining that the venous pressure is abnormally high was originally described by Gaertner.<sup>12,14</sup> With the patient sitting and relaxed, the superficial veins of the hand are watched

for collapse while the arm is slowly raised. The distance of the point at which collapse is observed from the plane of the right atrium (taken as the fourth intercostal space) is a rough measurement of the venous pressure. Normally, it is equivalent to 100 mm of water.

In a third technic the veins on the undersurface of the tongue are inspected while the patient is sitting.<sup>15</sup> When the venous pressure is equivalent to more than about 200 mm of water these veins are obviously distended; normally, they are collapsed.

The inspection procedures described above afford a rough qualitative means for evaluation of the venous pressure, mainly in cases of heart failure. When the findings are positive it is fairly safe to conclude that the venous pressure is higher than normal, although rather wide variations of degree cannot be assayed. When the findings are negative

look the fact that distention of the superficial veins more frequently indicates local obstruction of the deep veins than vice versa. An excellent example of this tendency is in cases of varicose veins of the lower extremities, which the physician often treats as a cosmetic problem without troubling to decide whether or not they are a consequence of deep venous occlusion.

### *Indirect Method*

The indirect method of measurement of venous pressure no longer has wide popularity, although it was extensively employed by Eyster<sup>1</sup> and a few other workers.<sup>16</sup> It depends on the principle that the least pressure necessary to cause collapse of a vein is approximately equal to the pressure within its lumen. The main advantage of this method is that since venipuncture is avoided it can be used

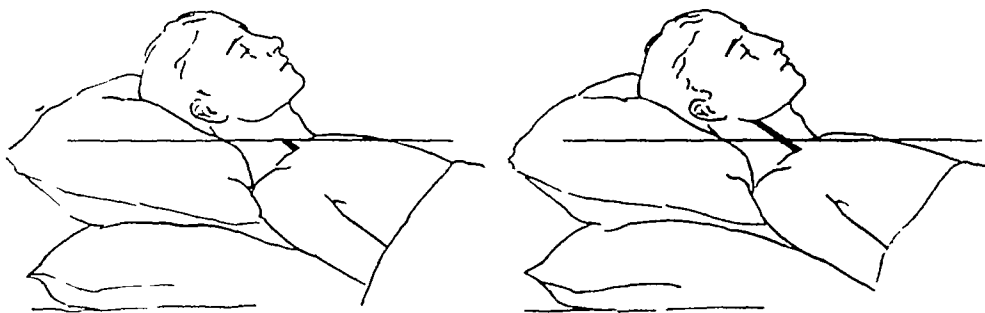


FIGURE 1 Normal and Distended External Jugular Vein

The sketch on the left demonstrates an external jugular vein normally filled, that on the right shows an external jugular vein filled to an abnormal height as a result of increased venous pressure (reproduced from Hussey<sup>12</sup> by permission of the publisher)

it is not safe to conclude that the venous pressure is within normal limits. This is true because a patient with heart failure, for example, may have a high venous pressure while supine and normal venous pressure while sitting.<sup>3, 4</sup> Elevated pressure of long duration is more likely to show clinically detectable venous distention than when it is of recent onset. Superficial veins in elderly persons are occasionally sclerotic and do not readily distend or collapse with variations in venous pressure.

Inspection of the superficial veins is a much more reliable diagnostic aid for detection of localized venous obstruction. The pattern of the superficial veins in the distribution of the collateral circulation of the obstructed vein contrasts so distinctly with the appearance of the superficial veins elsewhere that suspicion of the diagnosis is obtained with the first glance. Two words of caution may be valuable regarding this point. In the first place, there are considerable differences in the visibility of the superficial veins of different persons, depending on the quality of the skin as well as anatomic variations in the venous pattern. It is important to remember, therefore, that the superficial veins must be distended, not merely visible, before they are accepted as evidence of localized venous obstruction. Secondly, there is probably a great tendency to over-

frequently and painlessly in the same patient. This advantage is outweighed by many disadvantages, including the difficulty of learning to use the apparatus skillfully, the failure of the test when the superficial veins are sclerotic or not visible and the fact that the venous wall may manifest hypertonus in some cases of heart failure.

### *Direct Method*

The direct method is the one most generally employed when results more accurate than those that can be obtained by simple inspection of the veins are desired. It consists essentially of measuring the venous pressure through a needle that has been inserted into the vein. A variety of instruments have been devised for this purpose.<sup>12, 17-27</sup> Most of them adopt the principle of a liquid manometer so that the measurement is represented directly as millimeters of physiologic saline solution, the liquid usually employed. An apparatus of this type that has given satisfaction during extensive trial is shown in Figure 2. This instrument is sterilized by boiling or autoclaving before it is used. It consists of a glass measuring tube (A) having a 3-mm or 4-mm bore and attached by rubber tubing to a three-way stopcock (C). Affixed to the appropriate adapters of the stopcock are a 5-cc or 10-cc syringe (B) con-

taining sterile saline solution and a 19-gauge or 20-gauge needle 3.7 cm long (D). The rubber tubing and glass are filled from the syringe, and the stopcock is then turned so that solution from the syringe can be injected into the vein to be punctured. If the venous pressure only is to be measured, the syringe is left partly filled with saline solution. If the circulation time is to be measured as part of the procedure, the syringe is filled with the agent used for this purpose. After venipuncture the stopcock is turned to the position that permits the solution to enter the vein from the measuring tube. Details regarding the position of the patient and

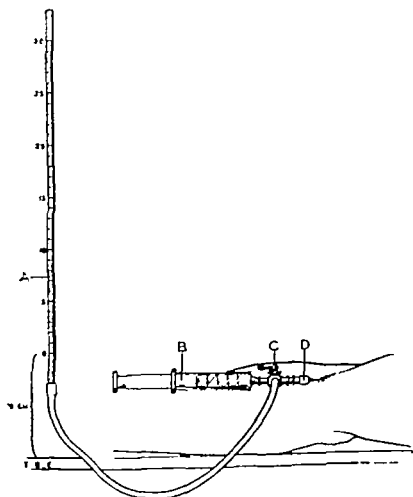


FIGURE 2. Apparatus for Measurements of Venous Pressure (Reproduced from Hussey<sup>23</sup> by Permission of the Publisher)

other essentials of technic during the procedure have been discussed above. For the moment, it is sufficient to say that the column of liquid in the measuring tube fluctuates lazily with respiration and sometimes sharply with the arterial pulse. The introduction of a needle into the vein may produce a temporary venospasm, which tends to raise the venous pressure. Ordinarily, the effect disappears within so short a time as to be a negligible factor. The tendency of the initial high value to drop to a constant level has been called "venous pressure drift."<sup>23</sup>

The apparatus described, although entirely suitable in hospital practice, is not completely satisfactory for routine use as a part of the examination equipment of the average physician. With this consideration in mind Burch and Winsor<sup>2</sup> have devised the "phlebomanometer." This instrument adapts

the principles of the aneroid manometer used clinically for recording arterial blood pressure to a manometer sensitive enough to register venous pressure. It is compact and portable and appears simple enough to be popular.

The instruments for direct measurement of venous pressure can be used in any accessible vein. The discussion presented below indicates that in some cases it is desirable to compare measurements in several different veins in the same patient. In the lower extremity the best vein for such comparisons is the femoral.<sup>24, 25</sup> This vein is punctured according to the technic of Griffith, Chamberlain and Kitchell<sup>18</sup> by insertion of a needle upward and inward at a point 2.5 cm distal to the inguinal ligament and just medial to the pulsation of the femoral artery. No tourniquet is required. The angle that the needle makes with the skin of the thigh and the depth to which it is introduced must be varied with the thickness of the tissues overlying the femoral vessels. For almost all cases a needle 3.7 cm long is adequate.

Other veins in the lower extremity than the femoral may be utilized for venous-pressure determinations. A number of French clinicians favor the use of the greater saphenous near the femoral triangle in place of the femoral vein.<sup>26-30</sup> If the greater saphenous vein at a lower level or the dorsal pedal vein is used, due consideration must be given to the gradient of pressures the more distal the vein is located from the heart.<sup>3, 31</sup> For example, in a typical case the pressure of the dorsal pedal vein was 40 mm more than that in the greater saphenous vein at a higher level.<sup>3</sup> The problem of gradient of pressures has been well discussed by Winsor and Burch<sup>3</sup> and Burton-Opitz.<sup>31</sup> This pressure gradient also holds for the upper extremity. For example, the dorsal-metacarpal-vein pressure may be about 10 mm higher than that in the median basilic and 50 mm higher than that in the cephalic or jugular vein.<sup>3</sup> Measurements of the pressure in the popliteal veins have also been made in a study of the effects of localized obstruction to venous flow in the lower extremities.<sup>27</sup> For this purpose the patient is standing and the "local" venous pressure only is measured by means of a mercury manometer. The difficulties of technic will prevent this method from being used except for research. Venous pressure may also be determined in the internal or external jugular vein.<sup>32, 34</sup>

#### NORMAL VALUES

Normal values for venous pressure measured by the direct method have varied in the experience of different authors on account of technical differences in their studies. The principal reason, as mentioned above, has been the lack of uniformity for selection of the zero level for reference of the measurement. When the zero level is placed at a point 10 cm from the skin of the patient's back the venous pressure

in the arms is normally equivalent to 50 to 150 mm of saline solution<sup>2</sup> The values reported by Winsor and Burch<sup>3</sup> using a slightly different zero level were essentially the same Normally, the pressure in the femoral vein is usually about equal to or a little higher than that in the antecubital vein of the same person<sup>5, 24, 25</sup> In some subjects, particularly those who are obese, the femoral-vein pressure may be as much as 40 mm of saline solution higher than the antecubital pressure

According to Jacques<sup>26</sup> there appears to be little difference between venous pressures in adults and children when they are considered collectively and studied under the same conditions of technic Eighty-three per cent of measurements were equivalent

out evidence of heart failure Szekely<sup>35</sup> noted that some showed a pathologic response Presumably, these were cases of latent cardiac failure These studies in human beings are interesting in view of the demonstration by Landis<sup>36</sup> that experimental damage to the heart of the dog did not produce a rise in venous pressure until the effect of exercise was superimposed On the basis of his experiments Landis commented that this could explain the development of right-upper-quadrant pain and a palpable liver after exercise in a cardiac patient whose resting venous pressure is normal

When venous outflow from an extremity is obstructed locally, exercise of the extremity causes a progressive increase in venous pressure above the

TABLE 1 *Diagnostic Value of Regional Differences in Venous Pressures*

PRESSURE DATA	DIAGNOSIS
Diminished in all peripheral veins	Peripheral vascular collapse (shock), syncope.
Elevated in all peripheral veins	Right-sided and generalized cardiac failure, constrictive pericarditis (Pick disease), pericardial effusion, uniform loss of negative chest pressure (obstructive emphysema), Bernheim syndrome, varicose veins
Normal arm and elevated in leg veins*	Ascites, tympanites, pneumoperitoneum, pregnancy, hypernephroma and other tumors of kidney, with invasion of inferior vena cava, primary carcinoma of liver, with invasion of inferior vena cava, primary tumor of inferior vena cava, thrombosis of inferior vena cava, ligation of inferior vena cava masses in peritoneal cavity, solitary abscess in right lobe of liver, subphrenic abscess on right, echinococcus cyst of liver large tumor mass in right lobe of liver
Elevated in arm and normal in leg veins	Aneurysm of aorta, dilatation of aorta, lymphoma of mediastinum, metastatic masses in mediastinum primary tumor of mediastinal structures, abscess of mediastinum, thrombosis of superior vena cava
More elevated in one arm than in other and lower or normal in leg veins	Localized obstruction of axillary or subclavian veins due to exertion, pressure from neoplasm, cardiac failure, unilateral chest lesions (pleural effusion, pneumothorax, thoracoplasty), aneurysm of aorta (85% higher on left than on right), aneurysm of innominate artery (higher on right than on left), arteriovenous fistula of arm
More elevated in one leg than in other and lower or normal in arm veins	Arteriovenous fistula of leg, thrombosis of femoral or iliac vein
Dissociation between internal jugular vein and general peripheral venous system	Polycythemia or mass in neck or upper mediastinum (elevated pressure) thrombosis of lateral sinus (diminished pressure)
Elevated in portal vein and normal in arm and leg veins	Cirrhosis of liver obstruction of portal vein, obstruction of splenic vein, Chiari syndrome.

\*Also observed during abdominal operations

lent to between 80 and 130 mm of water Lambert<sup>27</sup> has also reported on venous-pressure values in normal children

RESPONSE TO EXERCISE

Venous-pressure response to exercise, under certain conditions, affords a means of enhancing the value of the determinations A reasonably extensive literature exists on this subject This has been reviewed by Szekely<sup>35</sup> A standardized technic for measuring venous pressure during and after exercise has been devised and gives reasonably consistent results<sup>35</sup> In normal subjects the venous pressure rises from 20 to 50 mm of water during exercise and returns to or slightly below the basal level within thirty seconds after cessation of the exercise<sup>35</sup> In patients with heart failure it rises much higher with exercise and returns to the initial level more slowly<sup>35</sup> This may be true even though the resting venous pressure of such a cardiac patient is normal In a group of patients with cardiac disease and with-

resting level, and return to this level is slow<sup>32, 37</sup> This technic can be readily employed when the upper extremity is involved<sup>32, 37</sup>

The exercise of the upper extremity consists of repeated clenching of the fist for one minute Normally, the venous pressure falls slightly or remains stationary except for minor fluctuations during the exercise Local obstruction anywhere from the axillary vein to the superior vena cava produces a steady increase in venous pressure during the one minute of the exercise test The magnitude of the rise varies from 10 to 900 mm of water<sup>32, 37</sup> This hand-clenching exercise is without effect in cardiac patients presumably because it is not strenuous enough to cause a general effect Similar results are obtained when the popliteal vein is used to test for obstruction of veins of the lower extremity or pelvis<sup>32, 37</sup> In constrictive pericarditis, the effect of local exercise (clenching fists) may be the same as in cases of local venous obstruction of the upper extremity in con-

trast to what is obtained in cardiac failure.<sup>22-24</sup> This has been noted in 3 typical cases.<sup>22-24</sup>

### HEPATOJUGULAR REFLUX

It was mentioned above that distention of the cervical veins in heart failure may become apparent for the first time when the patient's abdomen is firmly compressed. This phenomenon was originally described by Pasteur<sup>29</sup> and later by Rondot.<sup>40</sup> It has since been called the hepatojugular reflux and also the Pasteur-Rondot phenomenon. The use of this maneuver has been commented on by Fishberg<sup>41</sup> and extensively studied by Oppenheimer and Hitzig<sup>7</sup> and by Hitzig.<sup>22-24</sup> It depends on the fact that abdominal compression quickly increases the return of blood through the inferior vena cava from the congested viscera, especially the liver, so that, in a sense, there is competition of this augmented flow with blood arriving from the superior vena cava. Because the heart is failing, the increased venous return is not accommodated, and consequent stagnation of blood in the superior vena cava is reflected as an increase in venous pressure in the tributaries of this vessel.<sup>7</sup> The same effect may be expected when there is a general increase in venous pressure from some other cause, such as constrictive pericarditis or pericardial effusion. When the superior vena cava is extensively obstructed the same phenomenon is observed, although the mechanism is different.<sup>22-24</sup> Here the effect of compression of the abdomen is to impede flow of blood through the inferior vena cava. Since in this syndrome this is the main route for ingress of blood from the superior-vena-cava system as well, pressure rises in the veins of this system. A similar result is obtained when the large superficial collateral veins of the trunk are occluded by means of a band encircling the thorax.<sup>22</sup>

For obvious technical reasons the influence of abdominal compression on venous pressure can best be evaluated by direct measurement. When an initial reading of the venous-pressure measurement has been obtained by the technic described above, the examiner compresses the patient's abdomen, preferably the right upper quadrant, for one minute. Care is taken to apply the compression gradually so that there will be no interference with the rate, rhythm or depth of respiration and no tendency for the patient to tense his muscles. Normally, with the maneuver, the pressure in the antecubital vein remains unchanged or falls.<sup>2-4, 22</sup> This effect is explained by the fact that curtailment of venous return from the inferior vena cava encourages a more rapid emptying of the superior-vena-cava system. In conditions causing general elevation of the venous pressure above normal and in the superior-vena-cava syndrome, the maneuver causes a rise of 10 mm. or more of water in the arm vein pressure. It is of considerable diagnostic importance that in cases of mild or latent heart failure the same effect is obtained,

although the venous pressure initially may be within normal limits.<sup>2-4, 22</sup> It has also been demonstrated that the venous pressure in the arms rises 30 mm. or more in patients with heart failure when the legs are raised from the bed while the trunk remains horizontal (Azoulay position).<sup>22-24</sup> This finding has a significance equivalent to the hepatojugular reflux.

### RELATION OF SPINAL-FLUID TO SYSTEMIC VENOUS PRESSURE

It is well established scientifically that a close relation exists between spinal-fluid pressure and cerebral venous pressure.<sup>45</sup> Except under certain rare conditions in which there is a dissociation between the internal jugular-vein and arm-vein pressures, which is discussed in greater detail below, the cerebral venous pressure reflects the general systemic venous pressure<sup>46-47</sup> or occasionally the pressure existing in the superior-vena-cava system.<sup>22</sup> A number of practical points about this relation are frequently overlooked in clinical practice.

The spinal-fluid pressure is increased in any of the conditions listed under the heading "elevated venous pressure in all peripheral veins" in Table 1 and in any other disease referred to in the table that involves the venous return through the superior vena cava. Harrison<sup>48</sup> found in normal people, as well as in patients with cardiac failure and elevated venous pressure, a definite ratio of spinal-fluid pressure to venous pressure that averaged 1.6. Therefore, if a spinal-fluid pressure is found to be elevated and no central-nervous-system disease appears to be the cause, a check on the arm-vein pressure is indicated. Increased spinal-fluid pressure secondary to high venous pressure has been suggested as the cause of a number of central-nervous-system manifestations.

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY, M D, *Editor*

BENJAMIN CASTLEMAN, M D, *Associate Editor*

EDITH E PARRIS, *Assistant Editor*

### CASE 33471

#### PRESENTATION OF CASE

A sixty-four-year-old man entered the hospital because of pain in the left flank

Eighteen years before admission the patient was told that he had bilateral kidney stones. Since that time frequent x-ray studies had been made, and the stones did not appear larger. He felt reasonably well until a year before entry, when he began to have malaise, anorexia, pallor and twinges of pain in the left flank. This pain became more frequent and severe, and for the previous month had been constant. It radiated from the flank to the lower back and groin and down the anterolateral aspect of the left thigh. There was nocturia (two or three times) and questionable hematuria.

The past history was irrelevant except for meningitis at the age of sixteen years, which had left the patient partially deaf in the right ear.

Physical examination revealed a thin, sallow man with a large, firm, tender, fixed mass in the region of the left kidney and a soft, apical systolic murmur. Neurologic examination disclosed bilateral Babinski reflexes, bilateral clonus, hyperactive reflexes, absent vibration sense at the right ankle, facial palsy on the right and Hoffmann's sign on the right.

The temperature was 100°F, the pulse 100, and the respirations 20. The blood pressure was 125 systolic, 70 diastolic.

Examination of the blood revealed a white-cell count of 15,600 and a hemoglobin of 7.5 gm. The urine gave a + test for albumin, the sediment contained only an occasional red and white cell per high-power field. The nonprotein nitrogen was 41 mg and the total protein 6.4 gm per 100 cc, and the alkaline phosphatase 5.7 Bodansky units. The carbon dioxide, chloride, calcium and phosphorus were within normal limits.

A plain x-ray film showed bilateral, irregular, stag-horn calculi (Fig 1). On the left side there was also irregular calcification overlying the lower pole of the kidney. There were several smaller areas of calcification in the right paravertebral region and pelvis, one of which was in line with the ureter.

A cystoscopy with ureteral catheterization and retrograde pyelography was done. The bladder

showed numerous calculi lying over the floor and a rather marked trabeculation. At the vesical orifice there was some enlargement of the median portion of the prostate. The left ureteral orifice was catheterized without great difficulty, but after the catheter had ascended to the upper ureter, it could not be pushed through into the renal pelvis and no drainage of urine occurred and none could be

The patient was given a total of 2500 cc of whole blood, which finally raised the hemoglobin to 11.4 gm. An operation was done on the tenth hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. F. A. SIMEONE This is the story of a sixty-four-year-old man who had calculi in both kidneys for ten years, but who had no symptoms from them, from an associated lesion or from an entirely new lesion until one year before entry. During this year he began to have malaise, anorexia, pallor and twinges of pain in the left flank. Taking for granted that he had stag-horn calculi and a few smaller calculi in the renal pelvis, these attacks might represent the repeated passage of small stones, perhaps culminating in increasing infection and possibly total obstruction of the kidney. The pain radiated from the flank to the lower back and



FIGURE 1 Plain Film of the Abdomen

aspirated. On the right side a catheter passed easily to the kidney, and the passage of the catheter was followed by rather clear urine.

Retrograde pyelography on the right side showed opaque material in the lower group of dilated calyces surrounding the calcification here as well as that in the kidney pelvis (Fig 2). None of the material was seen to enter the upper group except possibly in one infundibulum. The group of calcifications in the midabdomen was outside the ureter. A small bit of calcification in the right pelvis was probably within the distal ureter, which was slightly widened. On the left side the opaque medium also projected into the lower group of calyces and extended into the calcification in the lower pole. Medial to the left renal pelvis the dye was seen as mottled, irregular areas of increased density. None was seen in the ureter.

Cultures of urine from the bladder and right kidney were negative.



FIGURE 2 Retrograde Pyelogram of Left Kidney

groin and to the anterolateral aspect of the left thigh. In the presence of a fixed palpable tumor in the left flank, this distribution of pain does not help further in the diagnosis but suggests that the mass was impinging on the lumbosacral plexus thereby explaining the radiation of the pain into the thigh.

The past history was irrelevant.



In the physical examination the important point was the large, firm, tender, fixed mass in the left kidney region. I do not believe that the soft apical systolic murmur was of significance, particularly in the presence of anemia. Many neurologic signs were described, but I am unable to connect them with the lesion in the flank. If it was a tumor, I do not believe that we can assume that there were metastases to the brain on the basis of the findings given. What seems more probable is that the signs represented pyramidal-tract disease as a result of the arteriosclerosis.

The slightly elevated temperature and pulse rate are consistent with an inflammatory lesion in the region of the left kidney, although a malignant lesion is not ruled out, because even in the absence of demonstrated necrosis in the tumor, renal tumors or other large tumors in that region might be accompanied by febrile reactions. Examination of the blood showed a leukocytosis, which is again consistent with an inflammatory lesion, but does not rule out the possibility of a malignant lesion. The hemoglobin of 7.5 gm per 100 cc, or approximately 50 per cent of what it should be, might be attributed to the urinary-tract infection for a matter of years, which we know this man had, and perhaps to the occasional bleeding into the urine as suggested by the questionable hematuria. There was a slight amount of albumin and only an occasional red and white cell per high-power field. The interesting point about that finding is that the urine did not disclose more abnormalities. The nonprotein nitrogen of 41 mg per 100 cc suggests some decrease in the function of the kidneys. The alkaline phosphatase was perhaps within the upper limits of normal. I do not believe that it suggests bone metastases. The calcium and phosphorus concentrations in the serum were within normal limits, which should rule out hyperparathyroidism.

We finally come to the x-ray examination, which yields more definite information. In the first place there were stag-horn calculi bilaterally, and on the left side irregular calcification overlying the lower pole of the kidney. There were several smaller areas of calcification in the right paravertebral region, one of which was in line with the ureter. As described, this makes one wonder whether the lesion was tuberculosis. There is nothing to suggest psoas abscesses with calcification in them. No mention is made of bone disease on x-ray examination, which one would expect under such circumstances. Since an intravenous pyelogram is not recorded I shall assume that it was not done, perhaps because the renal function was not considered adequate to yield a satisfactory pyelogram.

A cystoscopy was done and it gave some specific information. Irregular calculi were found in the floor of the bladder and these perhaps came down from the calyces of the kidney and may have come from the lesionable area, thereby accounting for the

twinges of left-flank pain that the patient had had during the preceding year. The enlargement of the median portion of the prostate is not particularly remarkable except that it helps to explain why these calculi were not passed from within the bladder.

We have the statement that the left ureteral orifice was catheterized without difficulty, but after the catheter had ascended to the upper ureter it could not be pushed through into the renal pelvis. No drainage of urine occurred, and none could be aspirated. That suggests an obstruction, perhaps in the upper ureter or at the ureteropelvic junction. Furthermore, however, on injection of a contrast medium some of the material did get into the pelvis, into the lower calyces and actually into the region that contained the calcification. It is rather difficult to understand this obstruction to the passage of a catheter into the kidney when no great obstruction was demonstrable to the retrograde injection of dye, and particularly since there was no mention that dye was seen in the left ureter. With a degree of obstruction great enough to prevent the passage of a catheter but not of injected fluid, one would expect some of the solution to reflux down the ureter.

Perhaps we should see the x-ray films now.

DR STANLEY M. WYMAN: The first few films are without dye. An additional point to be mentioned is the possibility of calcification in the left kidney. The calcification lies far lateral in relation to the lumbar spine. There is a suggestion of a mass overlying this portion of the abdomen contiguous with the kidney and perhaps displacing the calcification laterally. This is the calcification described overlying the lower pole. The next film shows the catheter right in the kidney pelvis. Again, the direction taken by the catheter suggests that the kidney is displaced. On the third film we see dye entering the right kidney and lying around the stone and outlining a normal ureter. The last film shows dye in the left kidney around the numerous small areas of calcification in the lower pole and also surrounding, to a slight extent, the large stag-horn calculus. The interesting part is this irregular distribution of dye. It represents perhaps the kidney pelvis and the area just above and medial to it. It is a lacy, irregular pattern of dye that suggests an irregular cavity of some sort, communicating with the kidney pelvis.

DR SIMEONE: Do you think that this dye could be extravasated outside the urinary passage?

DR WYMAN: I cannot say that it is not extravasated and lying free in the peritoneal cavity, but it seems unlikely. I should like to explain the displacement of the stone on some basis connected with this irregular accumulation of dye.

DR SIMEONE: We now come to a differential diagnosis. This man had a tender fixed mass in the left flank. One wonders about lesions in the organs immediately adjacent to the kidney, such

as the descending colon, the spleen and the pancreas, but I think that we can pass these up because we have no data suggesting that these organs have been involved. We might concentrate on a differential diagnosis of the possible lesion that could cause this picture arising from the kidney itself. Before I saw the x-ray films I thought of a number of possibilities, but the films themselves exclude many of them, such as a large parapelvic cyst, which might have calcification in its walls and

Another excellent possibility in this case is perinephric abscess. It would fit in with a certain group of cases associated with renal calculi of long standing. I do not believe that the history of several months' duration is against the diagnosis of the chronic type of perinephric abscess. Renal stones occasionally erode through the pelvis and actually through the renal parenchyma to cause such abscesses. In my mind, the possibilities lie between a carcinoma of the renal pelvis and a

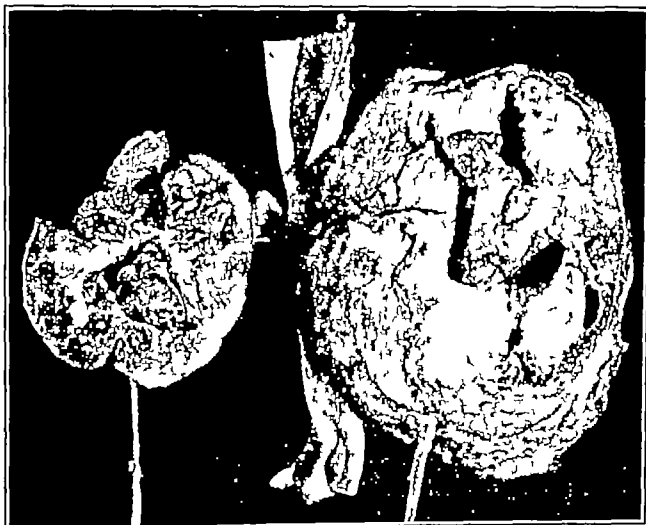


FIGURE 3

might connect with the renal pelvis. The question of tuberculosis also comes up. Tuberculosis does occur in association with stones in a fair proportion of cases at the age of this patient. It would be unusual that nothing was found in the bladder to suggest tuberculosis.

We come next to the question of tumor within the kidney comprising the major bulk of the mass and causing nonfunction of that kidney. Tumors of the renal pelvis, particularly of the nonpapillary type, do occur in association with stones within the renal pelvis and probably more commonly than in kidneys without stones. This is comparable to the greater incidence of carcinoma of the gall bladder in association with gallstones than in the absence of stones. Tumor of the renal pelvis causing nearly complete obstruction at the ureteropelvic junction is therefore a good possibility, and it might explain the failure to get urine from the catheter, since the kidney may have been nonfunctioning.

perinephric abscess. I favor the former diagnosis, a nonpapillary, squamous-cell carcinoma of the renal pelvis, associated with stones.

DR BENJAMIN CASTLEMAN: What did you think about this, Dr Colby?

DR FLETCHER H. COLBY: That is exactly the diagnosis that I should have made.

#### CLINICAL DIAGNOSES

Carcinoma of left kidney, perinephric abscess?  
Nephrolithiasis

#### DR SIMEONE'S DIAGNOSES

Squamous cell carcinoma of left renal pelvis  
Nephrolithiasis

#### ANATOMICAL DIAGNOSES

*Squamous cell carcinoma of left kidney, with extension into psoas muscle and with metastases to lung and liver*

Nephrolithiasis, bilateral  
Duodenal ulcers, multiple (four)

### **PATHOLOGICAL DISCUSSION**

DR CASTLEMAN Dr Leadbetter, will you describe the operative findings?

DR W F LEADBETTER, JR I operated with the expectation of finding either abscess or a degenerative tumor. It turned out to be the latter. It was a large mass that had extended behind and above the kidney, with involvement of the psoas muscle, and well into the connective tissue around the aorta. It was obviously a malignant tumor. I drained it, and there was a good deal of relief for some weeks.

DR CASTLEMAN Autopsy showed a large tumor of the left kidney, which weighed about 1200 gm. The tumor, as Dr Leadbetter has said, extended down into the psoas muscle and formed a fistula with the operative wound. The renal artery opened directly into the mass and was lost in it. The ureter was also imbedded in the mass and the proximal portion of the renal vein was filled with tumor. There was a stag-horn calculus, imbedded in a granular infiltrating tumor that originated in the pelvis (Fig 3). Microscopically, it was a squamous-cell carcinoma. The other kidney also contained calculi, and these were floating in foul green pus. There was one small metastasis to the right lung and a few small ones to the liver.

An incidental finding—and it is amazing that the patient had no symptoms from it—was the presence of four large duodenal ulcers, two in the first portion of the duodenum and two in the second portion, one of which extended to the ampulla of Vater. One had eroded into the pancreas, and another, the most proximal, formed a fistula with the neck of the gall bladder.

DR ISAAC TAYLOR Were the ulcers old?

DR CASTLEMAN No, fairly recent.

### **CASE 33472**

#### **PRESENTATION OF CASE**

*First admission* A seventy-six-year-old man entered the hospital complaining of intermittent periumbilical and left abdominal nonradiating pain of two months' duration.

The patient stated that the pain was dull "like a toothache" and located along a transverse area at the level of the umbilicus, primarily on the left side. There was no known predisposing factor, and there was no change in bowel habits, or melena. Vomiting occasionally resulted in relief of pain. At a community hospital the patient was told that he had jaundice although he had no itching or dark urine. X-ray studies at the hospital were said to have shown a possible neoplasm of the pancreas. During the preceding three months he had felt weak and tired and had an "all-gone" feeling.

Physical examination showed a well nourished man with a Grade II apical systolic murmur. A left direct inguinal hernia was present, abdominal examination was otherwise negative.

The temperature, pulse and respirations were normal. The blood pressure was 130 systolic, 90 diastolic.

Examination of the blood disclosed a hemoglobin of 14.5 gm and a white-cell count of 10,000. The urine showed a 0 to + test for albumin, with a specific gravity of 1.020, and 6 to 20 white cells per high-power field in the sediment. The nonprotein nitrogen was 26 mg per 100 cc, the protein 7.4 gm, and the chloride 100 miliequiv per liter. The prothrombin time was normal. A barium enema showed a few diverticula of the sigmoid but was otherwise not remarkable. An intravenous pyelogram and chest film revealed no significant abnormalities. A gastrointestinal series disclosed prominent lesser-curvature folds in the prepyloric area. The duodenum was deformed, and barium entered the biliary tree.

A sigmoidoscopy was negative. The hernia, which was indirect and contained adherent sigmoid posteriorly, was repaired. The patient did well postoperatively and was discharged four days later.

*Second admission* (six weeks later) The patient was readmitted because the midabdominal left-lower-quadrant pain had persisted, occurring several times a week, and had been accompanied by vomiting. Twice he had been jaundiced for about a week and had pale stools. Weakness, fatigue and anorexia had appeared. At times a brief "pressing, clamped feeling" had been noted across the epigastrium.

Physical examination was essentially as before. The herniorrhaphy incision was well healed.

A second gastrointestinal series showed the same findings in addition to a duodenal diverticulum. A cholecystogram revealed no filling of the gall bladder. Gastric aspiration demonstrated a + guaiac reaction and no free acid. The white-cell count was 13,600. The urine was normal, except for 30 to 40 white cells per high-power field in the sediment.

The blood chemical findings were normal, including a van den Bergh reaction. A serum amylase test was 7 units per 100 cc.

On the eleventh hospital day a cholecystectomy and choledochostomy were performed. The gall bladder was a mass of scar tissue, with the duodenum drawn up in the scar. The common duct was markedly dilated and contained stones and muddy material. No definite fistula was demonstrated. Postoperatively the systolic blood pressure was between 70 and 80 for seven hours. Two blood transfusions were given, with a gradual rise in blood pressure. Mild congestive failure was treated with digitalization. Prophylactic femoral-vein ligations were performed. On the fourteenth postoperative day the patient was discharged after a cholangiogram showed patent ducts.

**Final admission** (nineteen days later) Several days after discharge the patient began to vomit three or four times a day. Bile-stained material drained from the operative wound, but the stools remained brown and he was readmitted for study.

Physical examination showed a frail, dehydrated, uncomfortable man with a normal temperature. The lungs were clear and the diaphragm moved equally on both sides. The transverse right upper abdominal incision was indurated laterally, and pus and bile exuded from a sinus.

The white-cell count was 12,800. The urine was essentially normal. The nonprotein nitrogen was 41 mg and the protein 5.5 gm per 100 cc, and the chloride 80 milliequiv per liter. The prothrombin time was 22 seconds, with a control of 17 seconds. A van den Bergh reaction was normal, and the serum amylase was 48 units per 100 cc. Injection of the sinus tract showed a dilated obstructed common duct. A gastrointestinal series revealed thick antral folds but no duodenal defects.

A transduodenal choledochostomy about two weeks after admission disclosed no obstruction, but a pericholedochous abscess was encountered. A duodenal choledochal fistula was present. Postoperatively, the patient did well for a few days but then gradually went downhill. He vomited frequently, the vomitus being guaiac positive. X-ray films showed a narrow nonobstructed duodenum. The pylorus and duodenal loop could not be visualized. While barium was still in the duodenal loop Hippuran injection through the "T" tube revealed a considerably distended common duct, with some pooling near it. There was no certainty that the Hippuran passed through the duodenal loop and small intestine. The main radicle leading to the left lobe of the liver showed a constant, round, filling defect consistent with a retained common-duct stone. The nonprotein nitrogen rose to 96 mg per 100 cc, and the urine output fell. The white-cell count rose to 30,000. On the fourteenth postoperative day the patient fell out of bed and went into shock. He was treated with two transfusions, after which he rallied but gradually lost ground again, developing an irregular pulse and coma. He died four days later.

#### DIFFERENTIAL DIAGNOSIS

DR. FRANCIS D. MOORE: This patient had had so much surgery and so many events on various admissions that the *modus operandi* today will be to follow the same order as that in which he was presented to his physician.

In the first place, he looked well enough at one point so that someone wanted to repair the hernia. He could not have appeared seriously ill. I wonder how much of the story was extracted in retrospect.

He had pain "like a toothache," which has a little significance, meaning probably that it was not a smooth-muscle pain or pain resulting from colic, but was more

likely pain due to a space-occupying process, which could be either a neoplasm or sepsis. This was located in an area to the left of the umbilicus, which certainly suggests the pancreas. Furthermore, he had been told at another hospital that he had jaundice, although he had no itching or dark urine, and I am inclined to believe that the scleras were examined and that slight jaundice was noticed. X-ray studies at that hospital apparently showed something in the region of the pancreas. The patient had an "all-gone" feeling. In other words, he was beginning to have a systemic response to the process, whatever it was.

Then the left inguinal hernia was repaired. At these meetings it is easy to be too critical of what others have done. There is nearly always a good reason, although it may not be apparent. However, we should learn from the warning given in this case that hernias are sometimes misleading. Many patients with a hernia in the inguinal region that has been present for years suddenly experience trouble and come to the doctor. The reason is usually not found in the hernia. There is some other intra-abdominal process causing increased pressure or irritating the peritoneum, which makes the patient notice the hernia. In older people a complete study, prior to herniorrhaphy, is certainly justified. I imagine that the various x-ray films were taken, because the physicians were disturbed about repairing a hernia in this elderly man who had other evidences of disease. It was noted that barium entered the biliary tree—a finding that to my knowledge always coexists with structural disease in that area, I am interested in seeing the film.

DR. TOUFIC KALIL: It was probably a fluoroscopic finding. I do not see it recorded.

DR. MOORE: If the fluoroscopist saw barium entering the biliary tree, that is significant, even if the films are not spectacular. The most frequent cause of air entering the biliary tree is a cholecystoduodenal fistula, which results from a gallstone eroding through into the duodenum. It can also erode through the common duct, and a cholecystocolic fistula can form in the same way and produce the same picture. I have not happened to see other nonsurgical conditions cause it. Of course, surgical maneuvers can produce that picture. The duodenal diverticulum that was demonstrated is not the primary lesion, and its significance as a cause of symptoms or of difficulty of any sort is usually regarded as slight. In any event, in the face of gross roentgenologic evidence of disease around the lower end of the biliary tree, this patient had his hernia repaired and was discharged four days later, which seems to me too early for discharge. Is that correct?

DR. JOHN W. RAKER: That is correct.

DR. MOORE: The patient had a history that was consistent with pancreatic complications. He had x-ray evidence of gross organic disease, with de-

struction of the normal anatomy At the second admission this process was continuing its inexorable advance, he had been jaundiced, had pale stools and was having intermittent common-duct obstruction Other symptoms of a systemic nature were present

The second gastrointestinal series again showed the diverticulum There was no filling of the gall bladder with a cholecystogram Without further information it is hard to know whether that is significant, it probably indicates chronic inflammation of the gall bladder The white-cell count was elevated, indicating a septic process, the urinary sediment showed white cells The blood chemical levels were generally normal, and included a serum amylase of 7 units per 100 cc To my way of thinking, that is an unusually low serum amylase, and possibly indicates that the acinar cells of the pancreas were not functioning normally One sees that occasionally in late chronic pancreatitis, or in neoplasms of the head of the pancreas with chronically obstructed ducts The serum amylase later went back up to 48 units per 100 cc, and I do not know how to interpret that, possibly extra-pancreatic sources of serum amylase were responsible

On the eleventh day an operation was performed Before going on, let us see again if we get any help from x-ray studies done on the second admission

DR KALIL These films demonstrate the Hippuran injections through the postoperative tube

DR MOORE I do not know what the preoperative diagnosis was But I think in terms of smoldering chronic pancreatitis superimposed on cholelithiasis and cholecystitis — a combination not too unusual What was found was a gall bladder showing evidences of cholelithiasis The duodenum was drawn up to the scarred common duct, which was dilated and contained stones and muddy material In other words, the caliber of the cystic duct was such as to allow gallstones to pass into the common duct, producing obstruction enough to cause secondary pancreatitis There was no fistula demonstrated, which is not surprising, it is often difficult to find I should like to ask Dr Mallory if any note was made at any time regarding the appearance and feel of the pancreas

DR TRACY B MALLORY No, there were too many adhesions in the area

DR MOORE Femoral-vein ligation was done to keep the patient from dying of pulmonary embolism A cholangiogram was carried out, and the patient was discharged Let us see the films of the cholangiogram

DR KALIL This is the patent common duct, with the T tube in it

DR MOORE The third admission occurred very soon, only nineteen days later The patient had lost a good deal of ground systemically, and much bile had seeped through the wound There is no mention that the tube was still in place

The normal temperature is interesting It possibly had something to do with the patient's age, because there was an elevated white-cell count and considerable sepsis was found a few days later He had dehydration, as evidenced by the chemical determinations — a low chloride and a protein of 5.5 gm per 100 cc It is fair to assume that he had been rehydrated and that the protein went down as a result The van den Bergh reaction was normal, which is puzzling, but we shall see in a moment a possible explanation for that The serum amylase was 48 units per 100 cc — back to the normal range

Injections of the sinus tract showed a dilated, obstructed common duct I think that this was the film showing the obstruction on the distal end

DR KALIL It is a very abrupt ending of the opaque column, rather smoothly rounded, and the material filters down on both sides

DR MOORE The common duct is 2 cm in diameter There is something in the lower end, which could be a stone, but if it is a stone, it is a tremendous one It could well be a tumor mass

A transduodenal choledochostomy was done, presumably because of the lesion in the lower end, but nothing was found That was a surprise A percholedochous abscess was encountered There was still sepsis, and the duodenocholedochal fistula was present The original fistula was finally located and was not cholecystoduodenal but choledochoduodenal This accounted for the barium in the biliary tree seen on the first films

The operation did not relieve the fundamental disease, and the patient finally died Before death one more Hippuran injection demonstrated that the main radicle in the left lobe of the liver showed a filling defect consistent with stone We do not know what the pancreas felt like at the third operation — it was probably impossible to feel it because of obliteration of normal structures

The patient seemed to be suffering from liver failure The white-cell count rose to 30,000 On the fourteenth postoperative day he suffered a minor trauma and finally died

From the systemic point of view I believe that this patient had sepsis, nutritional depletion, dehydration and liver failure Did he have some fundamental process, such as carcinoma, that was causing the entire picture? He could have had a carcinoma of the pancreas, I somehow believe that more concrete evidence would have been found in two surgical attempts in the right upper quadrant If all this is blamed on carcinoma of the pancreas, it must be concluded that the obstruction to the duct was on that basis, and yet this was not so at operation

Could the patient have had lymphoma or some other bizarre neoplastic process masking the sepsis? Reticulum-cell sarcoma often acts in that way, but such a diagnosis would be just a guess because we have no histologic evidence There was an element of congestive failure Terminally, I think that he

had cholemia, the clinical syndrome of liver failure, which can co-exist with a surprisingly low serum bilirubin, which in this patient seemed to be normal most of the time, but we must not forget that one lobe may have been obstructed while the other drained reasonably well

What else could have caused the gradual downhill course? I cannot help thinking in terms of liver abscess. This patient had sepsis. We have no culture, but it may have been a virulent organism that was floating up and down the extrahepatic biliary tree for many months. The drainage was not adequate, and although liver abscess is much more commonly a blood-borne than a duct-borne lesion, I think that in this exceptional case, in which there was so much sepsis in and around the duct and evidence of at least anatomic obstruction of the duct, he may have had an abscess in the left lobe of the liver. If so, it would be less likely to show as a distortion of the diaphragm by x-ray study, because the left lobe of the liver is under the mediastinum instead of being under the free diaphragmatic structures.

My final diagnosis is heart disease, which I assume was arteriosclerotic in nature, with congestive failure, cholemia, sepsis around the common duct and liver abscess.

Dr. RAKER. One thing might be said about the hernial repair. The gastrointestinal series was originally interpreted as normal. The hernia was repaired, and it was not until after discharge that the final report came back showing this fistula.

Dr. MOORE. That is important. Such a delay happens all too frequently, simply because of a slow rapport between the services.

Dr. F. DENNETTE ADAMS. Why did you give up the thought—or rather why did you not concentrate on the thought—that the pancreas was involved as the result of chronic infection?

Dr. MOORE. One reason was that an amylase of 7 units per 100 cc was recorded, and the level went back up to 48 units within a few weeks. It makes it seem unlikely to me that a great deal of acinar tissue had been destroyed. There is no question that there was inflammation in the pancreas, but I doubt if a pancreatitis was the cause of the whole disorder. I have already mentioned my reasons for believing that although carcinoma of the pancreas was possible, it was an unlikely cause for the whole picture.

#### CLINICAL DIAGNOSES

Spreading peritoneal sepsis  
Cholecystitis, with cholelithiasis, postoperative  
Uremia

#### DR. MOORE'S DIAGNOSES

Arteriosclerotic heart disease, with congestive failure  
Cholemia

Chronic cholangitis  
Liver abscess

#### ANATOMICAL DIAGNOSES

*Adenocarcinoma of body of pancreas, with extension into and ulceration of stomach*  
Choledochoduodenal cutaneous fistula  
Pericholedochal abscess  
Peritonitis, localized  
Pneumonitis, aspiration type, bilateral  
Diverticulum of duodenum  
Diverticulitis and diverticulosis of sigmoid  
Operations: cholecystectomy, old, choledochotomy, recent and old, left inguinal herniorrhaphy, old, bilateral, superficial femoral-vein ligations, old

#### PATHOLOGICAL DISCUSSION

Dr. MALLORY. The findings at autopsy were complicated. There were many adhesions throughout the abdomen, particularly around the region of the common duct and duodenum, and I am sure that that is what prevented exploration of the pancreas. There had been an acute sepsis about the common duct, which had been pretty well cleared up by the last operation. We did find one pocket of retroperitoneal pus above the upper pole of the right kidney and between the liver and kidney. That was relatively small, measuring 2.5 cm in diameter. The fistula between the duodenum and the common duct was still present, and the ampulla was apparently perfectly patent, admitting a probe without difficulty. There was therefore no demonstrable obstruction of the biliary tract at the time of autopsy.

The heart showed a moderate grade of calcareous aortic stenosis, with considerable interadherence of the cusps and marked calcification, which would have prevented their complete opening.

The surprise of the autopsy was a large area of ulceration on the lesser curvature of the stomach, 4.5 cm in one diameter and 3 cm in the other. There was no suggestion of it in any of the x-ray studies. This was a deep ulcer, and the bed of the ulcer was formed by the pancreas. The pancreas seemed rather firm throughout but presented no areas of necrosis and no gross appearance of tumor. It was thought to be a chronic pancreatitis secondary to a penetrating gastric ulcer. When, however, we came to examine the microscopical sections, we were forced to change our minds drastically. Diffusely infiltrating through the pancreas was an adenocarcinoma, and the stomach was obviously secondarily involved by a cancer that was primary in the pancreas.

Dr. MOORE. It helps to demonstrate the truth of the old adage that if we lean too heavily on any one diagnostic aid—in this case x-ray examination—it may give way and let us down hard.

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## THANKSGIVING

IT HAS become a pleasant custom of the editorial writers of the *Journal* to comment on the annual return of certain significant holidays, and to recall what comfort or inspiration may be found in the occasion. The observance of Thanksgiving Day is particularly appropriate to this custom, for we think of our Thanksgiving, although a national holiday, as belonging especially to New England, where its celebration originated.

In 1621, after the first harvest of the Pilgrim Fathers had been gathered, Governor Bradford appointed a day of thanksgiving and prayer for the event. In 1623, during one of those extended droughts with which every New England farmer is familiar, a day of fasting and prayer was changed

into one of thanksgiving for the rain that fell even during the prayers that were raised in supplication for it. The Lord had let the light of His countenance shine upon the New World.

Soon all the New England colonies, by proclamation of their several governors, were observing a day of thanksgiving after their crops had been harvested and stored. The custom spread from New England. A Thanksgiving Day was annually recommended by the Continental Congress during the Revolution, and in 1864 President Lincoln inaugurated the custom, followed by each succeeding president, of proclaiming a general day of Thanksgiving for all the land.

Despite our tendency in this country to think of Thanksgiving as a uniquely American holiday (given to the rest of the nation by New England) there is no particular reason for cherishing a belief that the expression of gratitude, even to a higher power, had its origin in the Western Hemisphere. Noah, we are told, many years before the appearance of that other bold navigator, Columbus, erected an altar after his deliverance from the flood and offered thereon "of every clean beast and every clean fowl burnt offerings unto the Lord in Thanksgiving." The English, in November, 1588, thirty-two years before the Pilgrims set foot on Plymouth Rock, held their own first official Thanksgiving for the defeat of the Spanish Armada, with Queen Elizabeth in attendance.

So we too may recapitulate those facts for which we have reason to be thankful, but differing from the Pharisee who thanked God that he was not as other men nor even as the publican, preoccupied with his own humility. We may be thankful for that basic principle of equality that we recognize and cherish. We may be thankful that out of our abundance we are able and minded to help those from whom so much has been taken — that we, as physicians, are privileged for a while to carry the torch of learning and with it to kindle new fires in some of the lands where the light has come so close to extinction.

Let us be thankful at this season, not only for our possessions but for the desire to share them, not alone for security but for the courage to maintain it!

## STUDY OF THE RUBELLA SYNDROME

AN AMAZING fact in the annals of modern medicine is the recent discovery of the relation between maternal rubella and the occurrence of certain congenital defects in the fetus. Apparently unheard of less than a decade ago, it has, in a surprisingly short time, become common knowledge that infection of a mother with rubella in the first trimester of pregnancy will result, in a large percentage of cases, in the occurrence of such defects as cataracts, deafness, microcephaly, mental deficiency and congenital heart disease in the fetus.

Such sinister sequelae from a virus infection so benign as rubella is generally considered to be are disturbing, they serve to increase still further our growing respect for virus diseases in general, and their possible late effects. Why this particular train of events has been hidden so long is a matter of conjecture. The relative infrequency of rubella and its usually mild manifestations in the age group involved, as well as the time interval between cause and effect, are probable factors.

More information is necessary before we have a clear picture of the effects of virus infection in the early months of pregnancy. Additional cases must be studied in which congenital malformations in the fetus have followed rubella in the mother, of particular importance will be figures on the incidence of rubella in early pregnancy *without* fetal complications, and a searching analysis of other types of virus disease to determine if they, too, may be involved in such a catastrophic sequence.

To this end a year's study has been launched and financed by the National Society for the Prevention of Blindness, Inc., with the approval of the American Academy of Pediatrics, and questionnaires are being sent to obstetricians, ophthalmologists and pediatricians, seeking pertinent information on the subject. Data will be collected on four types of cases: children with congenital defects associated with rubella in the mother during pregnancy, children without congenital defects whose mothers had rubella during pregnancy, children with congenital defects associated with other maternal infections in the first trimester of pregnancy, and children with the so-called "rubella syndrome" (cataracts, deafness, microcephaly and congenital

heart disease) unassociated with any maternal infection during pregnancy.

The occurrence of any such cases should be reported to Dr. Herbert C. Miller, University of Kansas Hospitals, Kansas City, Kansas, the chairman of the committee entrusted with the study.

## MASSACHUSETTS MEDICAL SOCIETY

## DEATHS

BAUM — Ewald G. Baum, M.D., of Natick, died on October 22. He was in his sixty-third year.

Dr. Baum received his degree from George Washington University School of Medicine in 1911. He was the inventor of a milk bottle cap to protect bottle tops from contamination. He was a fellow of the American Medical Association.

His widow, two stepchildren, a sister, two brothers and a nephew survive.

KING — Frederick A. King, M.D., of Marshfield, died on September 14. He was in his seventy-ninth year.

Dr. King received his degree from Boston University School of Medicine in 1895.

Two sons survive.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

## MASSACHUSETTS STATE PLAN

The acute need for additional hospital facilities in this country resulted in 1946 in the enactment of Public Law 725, the Hospital Survey and Construction Act, by the Seventy-Ninth Congress. This act establishes a grant-in-aid program to assist the states to plan and build additional hospital and health-center facilities where they are most needed. In the next five years, under this program, total expenditures in Massachusetts alone will amount to twenty-four millions. Of this amount, a third will be allotted by the federal government and two thirds will come from state or local sources.

The Massachusetts plan for the administration of Public Law 725 is being developed in several stages. The first step consists of a survey of all existing hospitals and health-center facilities in the Commonwealth. After completion of the survey, the Commonwealth is divided into three categories of general hospital service areas designed as base, intermediate and rural, depending on population and the existing or proposed general-hospital facilities within the area. The next step is the determination of general bed needs by formulas established by the United States Public Health Service for each type of area that leads to the establishment of a priority schedule. The order of general-hospital projects built under this act must conform with this priority scheme. Finally, consideration is given to the determination of needs in the other categories of facilities — that is, tuberculosis, mental and ~~and~~ hospitals and public-health centers.



—by standards established by the United States Public Health Service

After approval of this plan by the State Advisory Council and the Surgeon General of the United States Public Health Service, a construction program will be developed for a five-year period in which federal funds will be distributed among the five categories of facilities mentioned above

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR SEPTEMBER, 1947

DISEASES	RÉSUMÉ		
	SEPTEMBER 1947	SEPTEMBER 1946	SEVEN-YEAR MEDIAN
Chancroid	2	1	1*
Chicken pox	123	110	106
Diphtheria	10	50	10
Dog bite	960	1079	924
Dysentery bacillary	14	5	17
German measles	43	56	49
Gonorrhea	393	443	410
Granuloma inguinale	0	0	0*
Lymphogranuloma venereum	0	1	1*
Malaria	7	25	13
Measles	69	204	168
Meningitis meningococcal	1	8	8
Meningitis Pfeiffer-bacillus	0	2	0
Meningitis, pneumococcal	1	3	1†
Meningitis, staphylococcal	0	0	0†
Meningitis streptococcal	1	1	0†
Meningitis other forms	1	0	1†
Meningitis, undetermined	10	1	2†
Mumps	148	101	194
Pneumonia lobar	31	37	106
Poliomyelitis	149	100	100
Salmonellosis	25	20	13
Scarlet fever	130	138	241
Syphilis	206	352	363
Tuberculosis, pulmonary	217	237	229
Tuberculosis, other forms	16	19	19
Typhoid fever	1	3	3
Undulant fever	10	1	2
Whooping cough	646	520	520
*Three-year median			
†Five-year median			

COMMENT

Diseases above the seven-year median were chicken pox, dog bite, poliomyelitis, salmonellosis, undulant fever and whooping cough

Diseases below the seven-year median were bacillary dysentery, German measles, gonorrhea, malaria, measles, meningococcal meningitis, mumps, lobar pneumonia, scarlet fever, syphilis, tuberculosis and typhoid fever

The downward trend of diphtheria has continued since June, 1947, so that it is now at the seven-year median. It is unlikely that this low prevalence will be maintained unless more energetic immunization programs are carried on.

Poliomyelitis is the highest recorded for the year — an incidence of 149 cases in September compared to 80 in August and 21 in July. The peak for the season appears to have been reached.

There is an indication that the upward trend in whooping cough, which had halted during the summer, is being resumed.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Ashburnham, 1, Bolton, 1, Boston, 7, Westfield, 1, total, 10.

Dysentery, bacillary, was reported from Boston, 1, Lexington (Metropolitan State Hospital), 6, Malden, 2, Salem, 2, Worcester, 1, Wrentham (State School), 2, total, 14.

Encephalitis, infectious, was reported from Salisbury, 1, Quincy, 1, Wareham, 1, total, 3.

Malaria was reported from Boston, 2, Braintree, 1, Everett, 1, Malden, 1, Seekonk, 1, Worcester, 1, total, 7.

Meningitis, meningococcal, was reported from Fall River, 1, Lowell, 1, Wellesley, 1, total, 3.

Meningitis, pneumococcal, was reported from Melrose, 1, total, 1.

Meningitis, streptococcal, was reported from Taunton, 1, total, 1.

Meningitis, other forms, was reported from Amesbury, 1, total, 1.

Meningitis, undetermined, was reported from Fall River, 1, Middleboro, 1, Newton, 1, North Attleboro, 1, Norwood,

1, Pittsfield, 2, Sheffield, 1, Wareham, 1, Wrentham, 1, total, 10.

Poliomyelitis was reported from Andover, 1, Arlington, 3, Athol, 1, Barnstable, 1, Becket, 1, Bellingham, 1, Beverly, 1, Boston, 23, Braintree, 1, Bridgewater, 1, Brockton, 2, Brookline, 9, Cambridge, 5, Canton, 1, Concord, 2, Dartmouth, 2, Dedham, 4, Egremont, 1, Everett, 1, Fall River, 7, Freetown, 1, Greenfield, 1, Hingham, 3, Lowell, 1, Lynn, 6, Marshfield, 1, Medford, 2, Middleboro, 2, Milton, 3, Natick, 2, New Bedford, 2, New Marlboro, 2, Newton, 3, North Brookfield, 1, Quincy, 2, Reading, 2, Revere, 1, Salem, 1, Saugus, 1, Sheffield, 2, Somerset, 1, Somerville, 2, Southbridge, 1, Springfield, 2, Sudbury, 3, Taunton, 3, Templeton, 1, Tewksbury, 1, Wakefield, 1, Waltham, 3, Watertown, 1, Wayland, 1, Wellesley, 2, West Bridgewater, 1, West Springfield, 1, Westport, 1, Weymouth, 1, Winchendon, 1, Winthrop, 1, Worcester, 10, total, 149.

Salmonellosis was reported from Andover, 1, Attleboro, 1, Boston, 2, East Bridgewater, 1, Gloucester, 1, Holyoke, 4, Lawrence, 1, Lowell, 3, Lynn, 1, Marblehead, 1, Medford, 3, Monterey, 1, Newburyport, 1, Salem, 2, Saugus, 1, Templeton, 1, total, 25.

Septic sore throat was reported from Amesbury, 1, Boston, 3, Haverhill, 1, Quincy, 1, total, 6.

Tetanus was reported from Brockton, 1, Great Barrington, 1, total, 2.

Trachoma was reported from Wakefield, 1, total, 1.

Trichinosis was reported from Boston, 1, Fall River, 2, Falmouth, 1, total, 4.

Typhoid fever was reported from Shrewsbury, 1, total, 1.

Undulant fever was reported from Bedford, 1, Belcher town, 1, Fitchburg, 1, Greenfield, 1, Holyoke, 1, Mansfield, 1, Palmer, 1, Somerset, 1, Warren, 1, Weston, 1, total, 10.

CORRESPONDENCE

NATIONAL PHYSICIANS COMMITTEE

To the Editor: A recent communication from the National Physicians Committee entitled "Factual Memorandum" says, "The source of the unremitting and relentless drive for Compulsory Health Insurance — Socialized Medicine — the Political Distribution of Medical Care in this country — is the Moscow dominated Communist Party of the United States."

The facts in regard to attempts to develop a National Health Program to be financed by compulsory health insurance are as follows. In 1938 President Franklin D. Roosevelt called a National Health Conference in Washington following which the first Wagner-Murray-Dingell Bill for Compulsory Health Insurance was introduced in 1939. This was followed by similar bills introduced by the same gentlemen in 1943 and 1945. On November 19, 1945, President Harry S. Truman requested legislation for adoption of a National Health Program, and at the same time Senators Wagner and Murray and Representative Dingell introduced a fourth bill entitled The National Health Act of 1945. Hearings were held on this bill before the Senate Committee on Education and Labor in the Spring of 1946, during the course of which Senator Taft supported by the American Medical Association and the National Physicians Committee introduced a bill entitled The National Health Act of 1946. Finally in the present Congress there are two health bills, one introduced by Senators Taft, Smith, Ball and Donnell in February, 1947, entitled The National Health Act of 1947, S. 545, and the other by Senators Murray, Wagner, Pepper, Chavez, Taylor and McGrath in May, 1947, entitled The National Health Insurance and Public Health Act of 1947, S. 1320. Thus it becomes apparent that both political parties now favor a National Health Program of some sort, and the question is, What will be the best program?

Both these bills of course are equally compulsory, the former requiring compulsory contributions to general taxes, and the other compulsory payroll contributions. Neither bill is compulsory as regards the receipt or the giving of medical services.

The main difference between the two bills is that the one favors the raising of the major part of the funds by the insurance principle from employed people and only using general tax funds to cover the needs of the unemployed. This eliminates the problem of administering a costly means

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test. It provides that the majority of people will be paying for their care and not getting free medicine. The other bill calls for the delivery of medical care paid for by taxes as charity after a means test has established the individual's eligibility. This means the recipients will be getting free care. As medical care is bound to become more expensive, this program will almost inevitably include an ever increasing proportion of the population. Even today fifty per cent of the people would probably claim and qualify for eligibility for part of their medical care. Thus the Taft Bill is just as much 'Socialized Medicine' as the Wagner Bill. Indeed Ex Governor Arnall characterizes it as Bismarckian state socialism of the most paternal type.

The idea of a National Health Program financed by Compulsory Health Insurance which was originated by President Franklin D. Roosevelt and furthered by President Harry S. Truman is now openly supported among others by the following groups of our citizens: American Association of Social Workers, Americans for Democratic Action, American Federation of Labor, American Veterans Committee, Congress of Industrial Organizations, Cooperative League of the United States of America, Council for Social Action of the Congregational Christian Churches, Methodist Federation for Social Service, National Association for the Advancement of Colored People, National Federation of Settlements, National Catholic Welfare Conference, National Consumers League, National Council of Jewish Women, National Council of Negro Women, National Farmers Union, Committee for the Nation's Health, Inc., Committee of Physicians for the Improvement of Medical Care, Inc. and The Physicians Forum Inc.

It must seem absurd to any intelligent person that two presidents of the United States and the above groups could be under the control of the Moscow-dominated Communist Party of America. It is hard for me to believe that the National Physicians Committee honestly thinks so. Therefore, I am forced to the conclusion that this Committee is either grossly ignorant of the facts or actually trying to mislead the medical profession. This suspicion that the National Physicians Committee whose actions have been approved by the House of Delegates of the American Medical Association knowingly circulates misinformation is strengthened by its actions in the past.

In the publications of the hearings before the Committee on Education and Labor, United States Senate, 79th Congress, Second Session on S 1606 Part 5, page 2679, seven quotations from the literature circulated by the National Physicians Committee are included and in each instance are proved false by quotations from the *Journal of the American Medical Association*. An example follows: "The statement by the National Physicians Committee 'The doctor would have little if any interest in the patient who is compelled to visit him'." Refutation by quotation from the *Journal of the American Medical Association*: "A patient may select any doctor." The other six misstatements recorded are as simply refuted by the *Journal of the American Medical Association* as the above. It is of interest that no denial of the accuracy of these senatorial records showing the falsity of statements by the National Physicians Committee has been forthcoming.

If the medical profession of this country wishes to form an honest opinion in regard to the relative value of the National Health Program under discussion it seems only fair that it should be permitted to judge the issue from statements of fact rather than from misrepresentations broadcast by the National Physicians Committee. Yet the tragic truth is that in the medical journals throughout the country with the exception of the *New England Journal of Medicine* and the *Official Journal of the American Academy of Pediatrics* little if any opportunity is offered for presentation of opinions other than those of the House of Delegates of the American Medical Association.

Physicians should be alert not to be deceived about the actual facts of proposed National Health Programs by the false statements of the National Physicians Committee. The subject is of vital importance to physicians. It deserves serious consideration not prejudiced propaganda.

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## BOOK REVIEW

*The Development of Inhalation Anæsthesia to the year 1846-1847* (Oxon) Publications of the Museum 8<sup>th</sup> cloth w/ Oxford University Press 1

The centennial of either an event or a location last year of several volumes such as Dr. Rapaport's *Johnson's Factory over Paris* and the a by the reference librarian for the to these the present volume, second publications by the Wellcome History is an official British history of the development of the use of the Nu. Anaesthesia of the University of Oxford tunity of research for this study and has att to trace the beginnings and to follow the those concepts and practices which have gone of the science and art of inhalation anaesthetic evolution." The volume is well illustrated with 26 lung is and sixty-one engravings presents a number from case topics in a series of five appendices and closes with a summary of events in the history of anaesthesia, Priestley's discovery of nitrous oxide in 1772 to hysema study in 1911 of ventricular fibrillation under chloro Dr. Duncan writes with authoritative scholarship. She made a distinguished and valuable contribution to medical history.

*The Psychoanalytic Study of the Child* Volume II 8<sup>th</sup> cloth 424 pp New York International Universities Press 1947 \$7.50.

This book is a collection of papers, some original and some revised on a wide variety of topics in psychoanalysis. The factual data concerning psychoanalytic findings and therapy in children or adolescents are meager in proportion to the quantity of strictly nonpediatric discussions and formulations. If the reader is to believe that in the book was gathered material for bringing up to date the workers in psychiatry and related fields in child psychoanalysis, the bibliographies at the end of each chapter (each presentation) are for the most part rather old. This gives the impression that each author has picked on a highly specialized topic on which to expound. Each paper is set apart from the others making the book uncohesive and many items are repeated. Some discussions are polemic—for example that on page 324 in which barbs are thrust at Klein, Adler, Jung and others.

The case reports were unusually well written, interesting and instructive. They illustrated the necessary titled features quite closely.

Although some of the material is new, much of the matter discussed has previously been presented in the periodic literature and standard texts concerning psychoanalysis. To the reviewer the book appeared to be an over-sized journal emphasizing by implication certain features of child and adolescent psychiatry.

*The Postnatal Development of the Human Cerebral Cortex* By J. LeRoy Conel M.D. Cambridge Massachusetts Harvard University Press. Volume I (1939) *The Cortex of the Newborn* 1<sup>st</sup> cloth 106 pp., with 2 tables and 194 illustrations \$8.00. Volume II (1941) *The Cortex of the Orientations* 1<sup>st</sup> cloth 136 pp., with 3 tables and 270 illustrations \$8.00. Volume III (1947) *The Cortex of the Three-Month Infant* 1<sup>st</sup> cloth 148 pp., with 6 tables and 219 illustrations \$12.50.

The first three volumes of this monumental contribution by Dr. Conel on the postnatal development of the human cerebral cortex begun in 1939 have been published by the Harvard University Press. The printing of these studies was made possible by a grant from The John and Mary R. Markle Foundation as well as by contributions from various research funds. The work has been conducted at Boston School of Medicine, Harvard Medical School Children and Infants hospitals in Boston.



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## THE PATHOGENESIS OF BRONCHIECTASIS\*

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BOSTON

SINCE Laennec<sup>1</sup> first described and named bronchiectasis its etiology and mode of development have been controversial issues. Numerous theories have been advanced, each of which is backed by voluminous evidence, but no one of which satisfactorily explains all types or features of the disease. Either the underlying cause remains undiscovered or multiple factors exist that predispose to or result in dilatation of portions of the bronchial tree. I propose, in the short time at my disposal, to review briefly the more significant of these possible factors and to compare their relative importance and interrelation.

Four important clinical and anatomic features of the disease must be explained by any theory of pathogenesis that can be considered satisfactory. First, bronchiectasis is rarely a diffuse disease of the bronchial tree. It characteristically involves a group of adjoining bronchi such as those of a lobe or a portion of a lobe—for example, the lingula of the left upper lobe. The affected segments of the tree may be, and frequently are, multiple but bronchi in the uninvolved areas are entirely normal.

Secondly, bronchiectasis is not usually a progressive disease. Most cases come under observation with well developed segmental involvement, and over months or years no extension to other portions of the bronchial system will be apparent unless an attack of pneumonia supervenes, when another segment may become involved.

Thirdly, bronchiectasis is rarely seen as an isolated finding in an otherwise normal lung. The surrounding pulmonary parenchyma is characteristically although variably abnormal. In the earlier literature, based primarily on post-mortem studies, acute and chronic pneumonitis was usually recorded, and Lord<sup>2</sup> was so impressed with parenchymal involvement that he preferred the term "bronchopulmonary sepsis" to bronchiectasis. In the present era, when lobectomy specimens are available from which to

study earlier stages of the disease, septic pneumonitis is unusual, but the surrounding lung is rarely normal. The changes vary widely from case to case, however, and may comprise atelectasis, fibrosis, organized pneumonitis, focal emphysema or even total destruction of alveolar tissue.

Fourthly, although bronchiectasis can develop at any age, it is characteristically a disease of youth. Onset in the first decade was recorded in 42 per cent of Perry and King's<sup>3</sup> series, and 69 per cent of their patients developed the disease before twenty years of age. With these four points in mind, the various theories of pathogenesis will be considered.

### CHRONIC BRONCHIAL INFECTION

Bronchiectasis is ordinarily associated with a chronic productive cough, and the sputum is characteristically abundant and purulent. In the days before modern contrast radiography with lipiodol instillation the evidence of bronchitis frequently preceded by long intervals the physical signs or x-ray appearance that would permit the diagnosis of bronchiectasis. Moreover, in autopsy or even resected specimens, evidence of chronic infection of the bronchial walls was almost uniformly present. The assumption that bronchial infection was primary and induced bronchial dilatation by injury to the skeletal structures of the bronchial walls, the musculoelastic tissues and the cartilaginous rings was not unreasonable. The chronic cough was thought by some to have a dilating effect on the bronchi, despite the fact, as Andrus<sup>4</sup> points out, that during cough the pressure is greater in the alveoli than in the bronchi, which therefore tend to be compressed rather than dilated. The deep inspiration preceding cough has, it is true, a bronchodilating effect but is of such brief duration that its effect is probably unimportant. The pressure of stagnant secretions was proposed by Laennec<sup>1</sup> himself as a dilating agent, but of course cannot be a factor in the "dry" types of bronchiectasis in which no secretion is present over long periods.

If ordinary bronchitis were a frequent cause of bronchiectasis one would expect the disease to be,

\*Part of a symposium on bronchiectasis presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1947.

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like emphysema, a geriatric rather than a pediatric problem. Many efforts have consequently been made to isolate specific organisms of exceptional virulence or of peculiar histolytic properties that would explain the extensive destruction of bronchial walls. Such attempts have been entirely unsuccessful.<sup>6</sup> The organisms found in bronchiectatic secretions are variable, numerous and usually mixed. Staphylococci, streptococci of numerous types and *Haemophilus influenzae* are usually present, spirochetes and fusiform bacilli are sometimes seen, and a wide variety of other organisms may be found from case to case and even from time to time in the same patient. Entirely similar flora may be observed in bronchitis without bronchial dilatation.

Careful pathological studies by Robinson<sup>7, 8</sup> of the affected bronchial walls in a series of lobectomy specimens showed the constant presence of severe inflammatory infiltration. Frequently, these infiltrates surrounded or invaded the scanty remnants of the musculoelastic tissues and the cartilaginous rings. These pictures were interpreted as evidence of active destruction of these elements by the inflammatory process. In a survey of lobectomy specimens I found severe bronchial inflammation of the type described by Robinson in 35 of 50 cases. In the remainder the inflammation was comparatively mild and in a case of so-called "dry bronchiectasis" was entirely absent. There was no close parallelism between the severity of inflammation and the degree of bronchial dilatation. Moreover, in a series of lungs from patients who had suffered from chronic asthma, in which no dilatation of bronchi was present and in which inflammatory infiltration sometimes exceeded that found in frank bronchiectasis, active necrotizing bronchitis was observed in only 3 cases. Its absence at the time of lobectomy does not, of course, deny the possibility of its existence in the past. When allowance is made for the stretching and atrophic effects of chronic dilatation it is doubtful if the evidence for active destruction of bronchial structures is adequate in most cases.

#### CONGENITAL ABNORMALITIES

The most important of the congenital abnormalities is the condition termed "congenital cystic disease." Outgrowths or buds of bronchial tissues from the trachea and major bronchi into the tissues of the mediastinum are not infrequent. These may produce cysts lined with ciliated or pseudostratified epithelium and may contain in their walls varying amounts of muscle, cartilage and glandular tissue. If the lumen of the stalk is obliterated they become distended with mucinous fluid.

That similar bronchial outgrowths that fail to differentiate into alveolar tissue may develop within the lung itself is not improbable, and lung cysts with or without connection with the lumen of bronchi have frequently been described.<sup>9-11</sup> The criteria for their recognition, however, are far from adequate,

and nearly all the features considered characteristic of congenital cystic disease are seen from time to time in bronchiectases that are almost certainly acquired. The existence of congenital cystic disease cannot be denied, but it seems probable that the diagnosis has been made far too frequently and with insufficient realization of how early in infancy and childhood acquired bronchiectasis may develop.

An indirect result of congenital influence is clearly shown by the cases of situs inversus with bronchiectasis of the lower lobe and coincident sinusitis.<sup>12</sup> The contention of Sauerbruch<sup>13</sup> that many patients destined to develop bronchiectasis have inherited bronchial defects is difficult to disprove but lacks positive supporting evidence.

#### BRONCHOSTENOSIS

Stenosis of major bronchi is frequently associated with progressive ectasia of the subtending divisions. Aspirated foreign bodies, intrabronchial tumors such as adenomas and slowly growing carcinomas, bronchial cicatrices due to syphilis or tuberculosis and peribronchial pressure from enlarged hilar lymph nodes, such as the primary complex of tuberculosis, have frequently been reported as initiating factors in the development of bronchiectasis.<sup>14</sup> Their influence cannot be denied, but the assumption of a direct causal relation is not necessarily valid. Fleischner,<sup>14</sup> in an interesting paper, reports 3 examples of bronchostenosis, the first associated with emphysema but no bronchial dilatation, the second with moderate ectasia but abundant purulent sputum and the third with extreme bronchial dilatation but no evidence of inflammation. Eloesser,<sup>16</sup> in a very thoughtful discussion of bronchostenosis, emphasizes the importance of Conner's<sup>16</sup> review of tracheobronchial syphilis. Although obstruction was present in nearly all cases only 15 per cent showed bronchial dilatation, and in 2 cases the bronchiectasis was limited to a portion of a lobe even though the stenosis was in the primary bronchus.

Another important group of cases to be considered in relation to the effects of bronchostenosis consists of the chronic asthmatic patients. In these patients functional narrowing of the bronchi exists over many years. In a group of 60 such cases that I have personally studied bronchiectasis was so exceptional that it appeared coincidental, although emphysema and cor pulmonale were of common occurrence.

Stenosis of bronchi, therefore, evidently does not regularly induce dilatation of the distal branches. If the obstruction is incomplete and expiration is impeded more than inspiration the alveoli rather than the bronchi tend to dilate, and emphysema results. With complete obstruction atelectasis follows, and this, as demonstrated below, is an important factor in the development of bronchial dilatation. Bronchostenosis, like obstruction in other duct

systems of the body, is also an important factor in the development and chronicity of infections, and infection of bronchi and of pulmonary parenchyma is another significant factor in the development of bronchiectasis. Finally, although a contributory role cannot be denied to bronchostenosis in many cases, the great majority of bronchiectatic lungs show no evidence whatever of narrowing of the bronchial tree proximal to the areas of dilatation.

### ATELECTASIS

To the radiologists and the pediatricians we owe a group of very important studies linking the development of bronchiectasis with persistent atelectasis.<sup>17-20</sup> Anspach<sup>17</sup> in particular has called attention to the frequency in infancy and childhood of a triangular shadow at the base of the lung field due to persistent atelectasis of a lower lobe or a large segment of such a lobe. Bronchograms following lipiodol injection regularly show dilatation of bronchi throughout this atelectatic area. In cases in which bronchoscopic drainage or other appropriate treatment is successful in relieving the atelectasis the bronchi may revert to normal. More frequently, however, the ectasia is already irreversible when first observed. Similar observations of reversible bronchial dilatation associated with atelectasis have been described by Singer and Graham<sup>21</sup> under the term "pseudobronchiectasis."

The mechanism by which atelectasis induces bronchial dilatation has been discussed in detail by Andrus<sup>4</sup> and others.<sup>22</sup> With collapse or destruction of huge amounts of pulmonary parenchyma a potential space is created within the pleural cavity, and the negative intrapleural pressure increases from a normal of -4 to -6 mm to figures as great as -30 to -40 mm. Numerous compensatory factors are brought into play. The chest wall is relatively rigid, but the diaphragm rises, the mediastinum shifts toward the affected side, and the neighboring pulmonary tissue overexpands. Despite these adjustments the intrapleural pressure remains more negative than normal, and this negative pressure is transmitted through the solid nonexpanded pulmonary tissue to the elastic and expandable bronchial walls. Here at last one finds an effective dilating force, which is constant for the duration of the atelectasis.

It must be emphasized that it is not atelectasis *per se* that tends to dilate bronchi but the effect of the exaggerated negative intrathoracic pressure. In therapeutic pulmonary collapse, when air is periodically introduced into the pleural cavity and negative pressures do not develop, pulmonary atelectasis may be maintained for long periods without danger of bronchial dilatation.

Strong opponents of the theory that atelectasis induces bronchiectasis are Tannenbergs and Pinner.<sup>23</sup> In carefully carried out experiments in rabbits atelectasis was produced by several means. Bron-

chiectasis did not develop unless the bronchi were simultaneously infected. It is by no means certain, however, that experiments on a small quadruped can fairly be used in drawing conclusions regarding man.

### PNEUMONIA AND OTHER FORMS OF PNEUMONITIS

In all reports of series of bronchiectatic cases histories of pneumonia or of upper respiratory infections frequently complicated by pneumonia, such as measles, pertussis and influenza have been obtained in 50 per cent or more of the patients (Ballon, Singer and Graham,<sup>21</sup> Perry and King<sup>2</sup> and Ogilvie<sup>22</sup>). Unfortunately, the nature of the pneumonic process can rarely be established from the available data. It is certainly unusual to see a typical pneumococcal pneumonia progress to bronchiectasis. In contrast, Opie and his associates<sup>24</sup> described the development of acute bronchiectasis following the 1918 influenza epidemic, and Kay<sup>25</sup> has recently reported 20 cases that were the sequel to atypical pneumonia in World War II. A significant number of patients trace the onset of their disease to a tonsillectomy, and another group to aspiration of foreign bodies — both common causes of septic pneumonitis. In autopsy and in resected specimens extensive inflammation of the pulmonary parenchyma is frequently observed, or patches of fibrosis may permit one to infer its presence in the past. In many cases, however, there is nothing to suggest the possibility of antecedent pneumonitis.

### DISCUSSION

Five factors — direct bronchial infection, congenital malformation of the bronchial tree, bronchial stenosis, pulmonary atelectasis and pneumonitis, with its sequel, pulmonary fibrosis, — have been discussed in relation to the pathogenesis of bronchiectasis. It has been shown that there is positive evidence to indicate a causal relation in certain cases for each of the five but that no one of them is

TABLE 1 Factors Present in 50 Cases of Bronchiectasis

FACTOR	TOTAL CASES	SEVERE GRADE	SOLITARY OCCUR REFERENCE
Bronchitis	49	35	0
Atelectasis	43	24	0
Pneumonitis	43	19	0
Fibrosis	40	3	0
Bronchostenosis	2	1	0
Emphysema	6	0	1

constant or can explain all cases. The complexity of the situation is shown by Tables 1 and 2, which were prepared from a survey of fifty unselected lobectomy specimens. No case considered to be of congenital origin appeared in the series, and bronchostenosis was present in only 3 cases.

It is evident from Table 1 that bronchial inflammation, atelectasis, active pneumonitis and fibrosis

were each present in 80 or more per cent of the specimens but that no one of these factors was constant and no one of them was ever a solitary finding unassociated with at least one other of the group. The combinations varied as is shown in Table 2.

It may safely be concluded that acquired bronchiectasis is generally a disease of the pulmonary

TABLE 2 Pulmonary Parenchyma in Bronchiectasis

COMBINATION	No OF CASES
Bronchitis, atelectasis, pneumonitis, fibrosis and emphysema	3
Bronchitis, atelectasis, pneumonitis and fibrosis	33
Bronchitis, atelectasis and pneumonitis	5
Bronchitis, atelectasis and fibrosis	2
Bronchitis, pneumonitis and fibrosis	3
Bronchitis and atelectasis	2
Bronchitis and pneumonitis	2
Bronchitis and fibrosis	1
Bronchitis and emphysema	1
Emphysema	1

parenchyma, as well as of the bronchial tree itself. This parenchymal involvement varies in detail, but one feature is common to all varieties: a noteworthy reduction in the number of aerated alveoli, potentially reversible in cases of atelectasis or early pneumonitis and certainly irreversible in cases of pulmonary fibrosis. Such a reduction in aerated parenchyma lowers the intrathoracic pressure and thereby generates an effective dilating force on the bronchial walls. The lack of aerated alveoli behind the involved bronchi renders cough ineffective as a mechanism for clearing bronchial secretions, since no current of air is generated, and stagnation of secretions becomes inevitable in dependent bronchi.

The assumption of primary bronchitis and secondary atelectasis with or without pneumonitis meets the test of the four criteria proposed above. Bronchial infection may cause atelectasis by obstructing the aeration of the alveoli with mucopurulent secretions. Infants and children are particularly prone to such obstructive atelectasis because the collateral air circulation through the pores of Kohn does not develop until adult life. They are also susceptible to pulmonary infections, in which bronchitis and atelectasis are more frequent than true pneumonic consolidation. Atelectasis is most likely to develop in the lower or middle lobes and in the lingula of the left upper lobe — the same distribution in which bronchiectasis is most usual. The most hopeful prophylactic measure in the prevention of bronchiectasis is therefore the prevention or prompt alleviation of atelectasis.

SUMMARY

Five factors — chronic bronchial infection, congenital abnormalities of the bronchial tree, broncho-stenosis, pulmonary atelectasis and pneumonitis or its sequel, pulmonary fibrosis — have been shown to be potential factors in the etiology of bronchiectasis. Of these, congenital cystic disease and broncho-stenosis are comparatively uncommon. Bronchial inflammation alone is rarely an effective factor but in combination with atelectasis or pneumonitis adequately accounts for most of the characteristic features of the disease.

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## AMEBIASIS

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NOW that World War II is over, it will be well to remember that a large part of the armed forces have seen service in areas heavily infected with *Endamoeba histolytica*. Most of these men and women have returned to their homes in the United States. A certain portion of them will have become infected with *E. histolytica*. The long incubation period of amebiasis, the comparatively mild nature of its symptomatology in many cases, the long period of symptom-free remissions and its tendency to recur merely emphasize the necessity that its presence be recognized. It is essential to realize not only that this disease may occur in returning veterans but also that cross-infection occurs in temperate zones and that the symptomless carrier, as well as the mild unrecognized case, serves as a reservoir of infection of the civilian population.

In the northeastern states amebiasis has always been endemic. Although several surveys of sample populations by the method of stool examination indicate that from 5 to 10 per cent of the people at some time harbor *E. histolytica* in their intestines, Faust<sup>1</sup> expressed the belief that an average incidence as high as 20 per cent, rather than the accepted figure of 5 to 10 per cent, may be reached in the United States. Table 1 presents the cases of amebic dysentery observed in Massachusetts from 1935 through 1945.<sup>2</sup> In 1944 and 1945 all cases but 1 were reported from the Army medical installations stationed in Massachusetts. In the years 1938–1939 Maine and New Hampshire reported only 1 case of amebiasis each. New York, in the same years, reported 153 cases. In 1937 Brenner<sup>3</sup> described 15 cases of amebiasis seen at the Peter Bent Brigham Hospital. In these cases one third of the patients had contracted the infection in New England.

That amebiasis is prevalent in the temperate zones and is not a disease limited to the tropical areas has repeatedly been emphasized. Judging by the paucity of reported cases in New England, one is led to believe either that the disease is not being recognized or that it is not being reported. It is our opinion that both beliefs are probably true. In any event, the war has created a much greater reservoir of people infected with *E. histolytica* who live in temperate zones. It is therefore considered timely to stress some of the clinical aspects of cases studied that are of value in the diagnosis of this disease. The clinical aspects of 60 cases of amebiasis seen in the Lovell General Hospital from January,

1945, to June, 1946, are presented below. The patients have been discharged from the Army and reside in the following states: Massachusetts (32 patients), Connecticut (12 patients), New York (7 patients), Maine (4 patients), Rhode Island (3 patients) and New Hampshire (2 patients).

The duration of symptoms varied from a few days to eleven years, one patient having had symptoms referable to the colon that had been present for the latter period of time. This case had previously been diagnosed as an "irritable colon." It was of interest that the symptoms occurred after a visit to the World's Fair in Chicago in 1933. There is some question, however, whether the symptoms were entirely due to amebic infestation, for in the last month they had become more marked. It was only at that time that stool examinations were done and cysts of *E. histolytica* found. There was a complete remission of symptoms following a course of Iodoquin. It would have required a longer period of observation, which was not possible in this case, to ascertain whether the symptomatology was entirely due to infection with *E. histolytica* or whether there was some underlying psychogenic disturbance. Symptoms were present for periods of less than three months in 12 cases and from three months to one year in 29. In 18 cases, symptoms were present for longer than one year.

The most frequent symptom was diarrhea (Table 2). In 25 cases the diarrhea was bloody. This varied from frankly bloody to merely blood-streaked stools. In a few cases there was rectal bleeding following defecation simulating that frequently seen in bleeding hemorrhoids. In 27 cases the stools were nonbloody, they were generally watery and brown. A fairly large percentage of these stools contained variable amounts of mucus. The severity of the diarrhea differed considerably. The number of stools varied from one to twenty a day. The patients often stated that the stools were normal between attacks of diarrhea. On close questioning, however, it was found that the stools were not of the same consistence as those prior to the onset of the diarrhea, but were somewhat loose and mushy.

The next most frequent symptom was abdominal pain. The pain was generally mild although in a few cases it was rather severe. In most cases it was low abdominal or periumbilical. It was generally described as crampy and was often relieved by defecation. In a few cases the pain was epigastric and closely simulated that of a peptic ulcer. In only 1 case was abdominal pain present without an associated diarrhea. In 7 cases there was a

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history of right-upper-quadrant pain All these patients had liver involvement and are discussed in detail below We have not included under abdominal pain 5 patients who complained of epigastric distress but have listed that symptom separately

Loss of weight was a prominent symptom, occurring in 11 cases The weight loss varied from 10

TABLE 1 Cases of Amebic Dysentery Reported from Army Installations, Civilian Hospitals and Private Physicians in Massachusetts

YEAR	TOTAL CASES	CASES REPORTED FROM ARMY INSTALLATIONS	CASES REPORTED BY PRIVATE PHYSICIANS AND CIVILIAN HOSPITALS
1935	12	0	12
1936	5	0	5
1937	5	0	5
1938	1	0	1
1939	3	0	3
1940	4	0	4
1941	4	0	4
1942	3	0	3
1943	1	0	1
1944	2	2	0
1945	18	17	1*

\*Retired veteran

to 40 pounds In these cases, 5 patients had amebic hepatitis, and 1 had amebic liver abscess The remainder had no involvement of the liver Six patients with and only 5 of the 53 without liver involvement showed weight loss In the latter group, 2 patients had concomitant recurrent malaria,

TABLE 2 Symptomatology in Amebiasis

SYMPTOM	NO OF CASES
Diarrhea	52
Nonbloody	27
Bloody	25
Abdominal pain	38
Nausea	11
Weight loss	11
Anorexia	9
Fatigue	6
Vomiting	6
Dyspepsia	5
Epigastric distress	5
Chills and fever	6
Constipation	3
Alternating diarrhea and constipation	2
Pain in rectum and coccyx	2
Joint swellings	1
Hemoptysis	1

which also probably played a part in the weight loss Nausea, anorexia and vomiting were the next most prominent symptoms Nausea and vomiting occurred only in association with either diarrhea or abdominal pain Less frequent symptoms were fatigability, dyspepsia, feverishness and chills The last two were present only in patients with liver involvement In 3 cases constipation was the only change in bowel habit and was not associated with diarrhea Chest pain, joint swelling and hemoptysis occurred as the presenting symptoms in 1 patient

with amebic liver abscess and bronchohepatic fistula In 2 cases the patients complained of alternating diarrhea and constipation

Physical examination offered little help in the diagnosis of amebiasis, except in patients with amebic hepatitis or liver abscess (These cases are discussed below ) A few patients had some tenderness in either the right or the left lower quadrant, or both, but it was hardly diagnostic In 1 case there was a perianal fistula In another there was evidence of bronchohepatic fistula with pulmonary involvement In no case were masses palpated Evidence of weight loss was present in 11 cases In the cases without hepatic involvement there was elevation of temperature in only 2 cases, the temperatures being 101 and 102°F

Proctoscopic examination was done in 47 cases There were minute mucosal hemorrhages of the rectum in 5 cases, in 2 of which trophozoites were obtained from scrapings In another case, cysts were observed in the stool but not in the scrapings In the 2 remaining cases, both stool examination and scrapings failed to reveal either cysts or trophozoites Seven cases showed the typical proctoscopic picture of amebic dysentery — namely, a sharply punched out ulcer crater, with undermined margins and with normal mucosa intervening In this group, motile trophozoites were obtained from the ulcers in 3 cases In 2, cysts were recovered The remaining patients failed to reveal either cysts or trophozoites Routine examination of the stools showed evidence of cysts in 1 case There were 8 cases of ulceration with generalized inflammation of the rectosigmoid mucosa in which scrapings from the ulcerated area failed to disclose cysts or motile trophozoites Cysts were found on routine stool examination in 3 cases, however, and the remainder showed neither cysts nor trophozoites In 1 patient, there was ulceration, with diffuse granulomatous changes Scrapings failed to reveal either cysts or trophozoites, and stools were repeatedly normal All these patients received active therapy, and repeated proctoscopic examinations were done on all, after the treatment there was complete healing

Reports of incidence of positive proctoscopic findings in amebic dysentery have shown marked variance Jackman and Cooper<sup>4</sup> observed lesions in 21 per cent of 115 patients Manson-Bahr,<sup>5</sup> on the other hand, found that 90 per cent of 258 patients had positive proctoscopic findings An intermediate figure of 42 per cent positive proctoscopic findings was reported by Browne et al<sup>6</sup> In our group of 60 cases 47 patients had proctoscopic examinations, and of these 43 per cent had positive findings

Repeated stool examinations were done on all patients The stools were examined by direct fecal film and also by the zinc sulfate flotation technic In many cases, the specimens were plated for isolation of *Shigella* organisms As many as fifteen stool

examinations were done on some patients. During proctoscopic examination, warm-stage microscopical studies were made of scrapings from the rectal or sigmoid mucosa for trophozoites.

Stools were positive in 46 cases. Of these, 38 showed cysts, and 8 disclosed motile trophozoites of *E. histolytica*. The location and forms of the organisms are presented in Table 3.

White-cell counts, which were taken on all the patients, ranged from 4000 to 10,000 in all cases uncomplicated by liver involvement, except in 1 in which the count was 12,000. The counts in cases of hepatic involvement are discussed below. The differential counts of white cells in the nonhepatic cases were within the normal range except for eosinophilia in 4 cases. The eosinophil count was 10 per cent in 2 cases and 16 per cent in 2 others.

Barium enemas were administered to 28 patients. In this group 19 patients failed to show any abnormalities, and 9 revealed changes on x-ray study. Of these, 2 disclosed spasticity of the entire colon, and 3 spasticity and irregular narrowing of the lower descending colon and sigmoid. One patient showed spasticity of the colon with loss of normal haustral markings to the hepatic flexure and with rigidity of the lower sigmoid. Cecal irregularity was noted in 4. Of the 9 cases with abnormal roentgenologic findings, there were cysts in the stools in 5. No motile trophozoites were found in any of these cases. Proctoscopic examinations in this group were positive in 4 cases, with pin-point hemorrhage in 2, ulceration with normal mucosa intervening in 1 and ulceration with generalized inflammation of the intervening mucosa in 1. In the cases with cecal irregularity, there was normal rectosigmoid mucosa in 3 and evidence of pin-point hemorrhage in 1. Stools were positive for cysts in 1 of these cases.

Considering the extent of literature published about amebic dysentery, comparatively little has been written about the roentgenologic aspects of the disease. Vallarino<sup>7</sup> was the first to call attention to the roentgenologic findings. More recently, Weber,<sup>8</sup> Bell<sup>9-11</sup> and Ikeda<sup>12</sup> have described the x-ray findings. These included varying degrees of irregular narrowing of the lumen of the large bowel. The cecum, which is the most frequent site of positive roentgenologic findings, is characterized by irregularity and deformity. An unusual degree of incompetence of the ileocecal valve, with rapid reflux of barium into the ileum, has been noted. The abnormalities suggest the findings in the ordinary type of chronic ulcerative colitis, aside from the changes of the cecum. There is a tendency, however, for the involvement to be less uniform and for abnormal segments of the bowel to be separated by what appears to be normal bowel. The wall of the large bowel is also relatively pliant and freely movable. The entire roentgenologic aspect of the disease is one of diminished intensity and severity

when compared with manifestations of other types of chronic ulcerative colitis. Amebic granulomas have also been described. There are irregular filling defects in the bowel very similar to carcinoma.

The incidence of positive roentgenologic findings in amebic dysentery varies considerably. Browne et al.,<sup>6</sup> reporting on the findings in 141 cases in which barium-enema roentgenologic studies were done, showed a 36 per cent positive roentgenologic change. Edson and his associates,<sup>13</sup> in a series of 20 cases, reported positive roentgenologic findings by barium enema in 80 per cent. Reeves, of Duke University, working with Ruffin of the same institute, in a series of 54 cases with *E. histolytica* in the stool, examined 19 patients by roentgenogram, and abnormalities considered to be indicative of amebi-

TABLE 3 Location and Form of *E. histolytica* in 60 Cases of Amebiasis

RESULT OF EXAMINATION	NO. OF CASES
Cysts found in stools	34
Motile trophozoites found in stools	5
Cysts found in proctoscopic specimen but not in stools	4
Trophozoites found in proctoscopic specimen but not in stools	3

asis were found in 68 per cent.<sup>11</sup> King, of Memphis, observed roentgenologic abnormalities in the large bowel of all 12 cases of amebic dysentery in which examinations were done.<sup>11</sup> In 3 of these cases, x-ray evidence first suggested the possibility of amebic dysentery, and this was later confirmed. In our group examinations on 28 patients revealed that 32 per cent had roentgenologic changes resulting from the amebic infestation of the large bowel. All cases with positive findings had repeated x-ray examinations after therapy, and in each case the findings returned to normal.

In our series there were 6 patients who were considered to have amebic hepatitis and 1 who had an amebic liver abscess. All these patients complained of pain in the region of the liver that varied from rather sharp and severe to dull and aching. Patients usually complained of pain in the region of the right costal margin, most frequently in the anterior or axillary region and at times posteriorly as well. In 1 case of liver abscess, the complaints and physical findings concentrated interest in the right lower pulmonary area. In 6 of the 7 cases there were acute temperature rises, which were intermittent in type and reached 103 to 104°F. Chills were present in 3 cases. Jaundice was observed clinically in 2 and in 1 was subclinical, the icteric index being 12.6. There was marked weight loss in 6 cases, varying between 10 and 35 pounds. Diarrhea was present in 4 cases on admission. One patient had no diarrhea on admission, but had had a positive history previously. The stools were bloody in 2 cases. The most important clinical

findings were hepatomegaly and marked tenderness over the liver. In 3 cases the liver could not be palpated because of extreme tenderness and rigidity. The spleen was palpable in 2 patients, both of whom had a history of malaria. The total white-cell count was elevated in all but 1 patient. The counts varied from 11,000 to 26,000, with a predominance of neutrophils. One case showed no elevation of white-cell count and no fever, but followed the low-grade symptomatic picture described by Castellani<sup>14</sup> and Hurst<sup>15</sup> and recently classified by Klatskin<sup>16</sup> as chronic hepatitis.

Stool examination showed trophozoites and cysts in 2 cases. In the remaining 5 the stools were normal. Proctoscopic examinations in three cases with negative stools disclosed no disease. Barium enemas were done in 2 cases but were negative. In 2 others complement-fixation tests for *E. histolytica* were positive. Neither of these patients had positive stools, and proctoscopic examination was negative in both. Liver-function tests in 1 case were normal. X-ray films of the chest were done in 4 cases. In 1 there was elevation of the diaphragm. In another a circular demarcated area of density in the posterior portion of the right lower lobe obscured the posterior sulcus and posterior half of the diaphragm.

There is little doubt that emetine is the drug of choice in amebic infestations of the liver. The response to emetine in cases of amebic hepatitis is quite dramatic. The amount used is generally between 0.4 and 0.8 gm. given parenterally in doses of 0.06 gm. daily. When 0.8 gm. is used it is wise to allow a short rest period after the seventh dose. Emetine in sufficient dosage is also the drug of choice in amebic liver abscesses, in which the amount needed is usually much larger. Most of the patients with amebic abscesses previously reported cured with emetine alone received between 0.6 and 0.8 gm. Klatskin<sup>16</sup> recently reported using the equivalent of 1.3 gm. of emetine in 7 cases of the early, acute type. This type of case responds better, generally, than the chronic abscesses. Payne<sup>17</sup> has recently reported, however, the successful use of emetine alone in large chronic abscesses. His 24 cases required an average of 2.4 gm. given over a period of one hundred and eight days. In 1 case he used 4 gm. in one hundred and twenty days.

The indications for aspiration are failure of the patient to show any improvement after 0.8 gm. of emetine and evidence that an abscess near the surface is getting larger under emetine therapy.

The indications for surgical drainage are rupture of an abscess into a serous cavity with the exception of rupture into the pleural cavity, when aspiration in addition to emetine may suffice, superficial abscesses located in the left lobe of the liver, and secondary bacterial infection of the abscess. In bacterial infection, which is an infrequent com-

plication, the use of aspiration, emetine and chemotherapy may eliminate the necessity of operation.

It is also believed that all cases of amebic hepatitis and abscess should be treated with one of the iodine-containing oxyquinolines. This is given usually after the course of emetine. Carbarsone, being an arsenic preparation, has been considered to be contraindicated in amebic liver involvement. This opinion, however, has been questioned.<sup>18</sup>

The treatment of acute or chronic amebic dysentery consists in the use of the following drugs in various combinations: emetine, carbarsone, chiniofon, Diodoquin and Vioform. There is considerable difference of opinion regarding which of these should be used and in what combinations. It is the belief of the majority that emetine administered parenterally, in addition to one or more of the enteric drugs, should be employed. D'Antoni,<sup>19</sup> however, has advocated the use of Diodoquin in doses of 0.63 gm. three times a day for twenty days, without emetine, and has reported 95 per cent cures.

The schedule used at this hospital consisted of 0.06 gm. of emetine daily for six days, 0.75 gm. of carbarsone being given concurrently each day for a week, followed by 1.8 gm. of Diodoquin daily for two weeks. We have also used Diodoquin as advocated by D'Antoni. The effect on the symptoms and laboratory findings was similar in both groups. Rarely were chiniofon or carbarsone enemas administered. We have not used chiniofon extensively, since it often produced rectal burning and severe diarrhea.

Recently, Lewis<sup>20</sup> has advocated emetine parenterally, as well as Vioform orally and in retention enemas in cases of acute and chronic amebic dysentery. The results of this regime in refractory cases have been excellent.

It is our opinion that the immediate results regarding symptoms and laboratory findings will be good in the majority of cases, whatever regime is used. In the refractory cases one may be forced to resort to many types of regimes to obtain good results.

We were unable to carry out any long-range studies on our patients, so that no attempt was made to determine the percentage of relapses. Just which type of treatment will result in the least number of relapses remains to be seen. Amebiasis is a disease in which treatment is difficult to evaluate, and it is often impossible to differentiate reinfections and relapses.

It is well to mention the toxic effects of emetine. There have been reports of death following therapy.<sup>21</sup> The toxic action is chiefly on cardiac and striated muscles. The patient receiving emetine should be on bed rest and should be examined each day by a physician, attention to any irregularity of pulse, soreness of muscles and fall of blood pressure being noted. If available, electrocardiograms should be taken before and during the course of treatment.

When doses of 0.42 gm. or less are used toxic effects are rare. When larger doses are contemplated, it is well to allow sufficient rest periods between courses.

### DISCUSSION

The diagnosis of amebiasis often requires extensive study. In many cases routine examinations of stools will reveal the presence of *E. histolytica* as the causative agent. In others, the correct diagnosis may be arrived at only by proctoscopic examination. The appearance of the rectosigmoid mucosa is often quite typical of amebic dysentery. In other cases, the disease is difficult to distinguish from ulcerative colitis due to chronic bacillary infection or that due to idiopathic ulcerative colitis. Scrapings of the ulcers should therefore be done, and the material examined both for the presence of motile trophozoites and cysts of *E. histolytica* in all cases, regardless of the appearance of the rectosigmoid mucosa.

X-ray examination of the large intestine often offers valuable information and may be the first clue that the patient has amebiasis. It also serves to eliminate other diseases, such as carcinoma, and thus has a twofold purpose. We have already described the roentgenologic findings in amebic infestation of the large bowel. Differentiation between amebic granuloma of the large bowel and carcinoma is often difficult. In some cases resections of portions of the bowel have been done with a preoperative diagnosis of malignant tumor, and the specimen has shown amebic granuloma of the bowel.<sup>23-24</sup> It is well to remember that carcinoma may also occur in patients with amebiasis. Reed and Anderson<sup>25</sup> have reported 4 cases with a long history of amebiasis and with lesions of the colon that were thought to be amebic and later turned out to be carcinoma.

Roentgen-ray differentiation of amebic granuloma and carcinoma of the large intestine has been emphasized by Bell,<sup>9-11</sup> who points out that the presence of associated abnormal findings in the cecum favors the diagnosis of amebiasis. When such findings are lacking, a therapeutic test is considered to be indicated if there is any associated clinical or laboratory evidence of amebiasis. Symptoms due to amebiasis show improvement after two weeks of antiamebic therapy.

The value of x-ray and fluoroscopic examination of the chest in cases with liver involvement with and without extension into the lung and pleura has been emphasized by Ochsner and DeBakey<sup>26</sup> and by Sodeman and Lewis.<sup>27</sup>

Demonstration of the etiologic agent in any disease places therapy on solid ground. The finding of cysts and trophozoites of *E. histolytica* depends on many factors: the ability of the examiner to recognize the presence of trophozoites and cysts in the stools, the number of stools examined and the type of examination. The examination of the

stools should be made as soon as possible after they are passed, since the trophozoites often die and disintegrate in the stools a short time after they are passed. Cysts should be searched for both by the iodine-stained or hematoxylin-stained films and by the zinc sulfate centrifugal flotation method. The study of purge as well as routine stools is of value. The value of scrapings of the rectosigmoid mucosa has already been emphasized. Nevertheless, a certain percentage of patients with amebiasis will not show either trophozoites or cysts. Sawitz and Faust<sup>28</sup> state that the ameba can be detected with the use of iodine-stained or hematoxylin-stained film, in combination with the zinc sulfate centrifugal flotation method, if five stools are examined, in between 70 and 90 per cent of cases. In our series the etiologic agent was demonstrated in 77 per cent of cases.

Sodeman and Lewis<sup>27</sup> have ably discussed the differential diagnosis and the importance of making an early diagnosis of amebic hepatitis. They were able to demonstrate *E. histolytica* in the stools of 55 per cent of cases of amebic hepatitis and 29 per cent of cases of amebic liver abscess. In our group of 7 cases we were able to demonstrate the causative organism in 2 (29 per cent). In 2 other cases with liver involvement, complement-fixation tests for amebiasis were positive. In both cases treatment was instituted before the results of the tests were obtained. Tests were done at the Army Medical School, Washington, D. C., and it took a few weeks for results to be returned. The complement-fixation test, no doubt, would be of value in cases suspected of amebiasis in which no definite ameba can be found, but as yet this test is not in common usage. We are in complete agreement with Sodeman and Lewis that the diagnosis of amebic hepatitis should be made on a clinical basis alone, even when laboratory examination fails to disclose the causative agent, which should nevertheless be sought for diligently.

D'Antonio<sup>29</sup> has subdivided amebiasis into the following clinical groups: asymptomatic, and symptomatic, including asyndromic and syndromic amebiasis, dysentery (acute or chronic), hepatitis and liver abscesses and involvement of other organs (abscesses of lung, brain and so forth).

We have not attempted to subdivide our cases into these classifications. No cases of asymptomatic carriers were included in our series. It has been our experience that the others often merge. A chronic case may suddenly show acute symptoms; in others, falling into the so-called "asyndromic" or "syndromic" group, the patient may have had dysentery in the past or may develop it in the future. We have listed our findings in patients with liver involvement, and also in 1 with liver involvement and secondary pulmonary involvement. One patient in the series showed a perianal fistula, which appeared at the time of the acute

dysenteric symptoms We have not seen involvement of other organs

In our group of patients 53 were from New England When one considers that this is only one Army installation, that many cases with mild symptomatology are not detected, that many others may have been in symptom-free remissions since discharge from the Army and that the incubation period of the disease may be quite long, it is logical to assume that amebiasis is not unusual in New England Of our group, 22 patients had received treatment prior to admission to the hospital and had relief of symptoms and yet had recurrences for which they were again hospitalized This is not to subscribe to a common adage "Once amebiasis, always amebiasis," but merely to emphasize that the disease recurs There is a variance of opinion regarding the frequency of recurrence Mateer,<sup>30</sup> using a single standard ten-day course of carbarsone and chinofon enemas, reported cure in 97 per cent of 104 patients followed from six months to three and a half years On the other hand, Lamb and Royston,<sup>31</sup> employing even more intensive therapy with chronic relapsing cases with a history of five months' to five years' duration, found that 91 per cent followed for nine weeks had relapses It is not the purpose of this paper to discuss the question of recurrences but merely to state that, in our observations, relapses have been quite frequent

In a certain group of patients with dysentery due to *E histolytica* no positive findings may be elicited by stool, proctoscopic or x-ray examination These cases present a difficult diagnostic problem and are often labeled irritable colon, mucous colitis and so forth In such cases the history often gives the clue Patients with psychogenic disturbances resulting in diarrhea often have a much older history, and psychogenic causes can often be demonstrated We also believe that any person who has previously had amebic dysentery, who complains of diarrhea and in whom no known cause for the diarrhea can be demonstrated should be considered as potentially having amebic dysentery and treated accordingly This policy could also apply to patients without a specific history of amebic infestation who have been in a highly endemic area and in whom likewise no cause for diarrhea can be found It has been gratifying to see a number of such cases completely clear up under therapy It is realized that patients with psychogenic disturbances of the bowel have been located in endemic areas and that the symptoms are not due to amebic infestation In these cases, however, one can generally obtain a definite psychogenic background, and little is lost even though therapy may be given with complete failure

We should also like to stress the similarity of the appearance of the rectosigmoid mucosa on proctoscopic examination in amebic dysentery and that

seen in both bacillary dysenteries and idiopathic ulcerative colitis Attention has been called to the fiery-red mucosa of acute bacillary infections and the discrete, undermined ulcers of typical amebic dysentery In the more chronic stages of amebic dysentery and bacillary infections, mixed secondary infestation with the colon bacillus, staphylococcus and streptococcus may so alter the appearance of the mucosa that its specificity is lost and the appearance is indistinguishable from that of typical ulcerative colitis We therefore believe that if there is a definite history of amebic infection and if stool cultures and examination fail to show a specific etiologic agent, antiamebic therapy is indicated, even though the appearance of the rectosigmoid mucosa suggests idiopathic ulcerative colitis We have seen 2 cases diagnosed as idiopathic ulcerative colitis in which the patients, who were given symptomatic treatment for six months without relief, showed complete clearing of symptoms and return of the rectosigmoid mucosa to normal when placed on antiamebic therapy

#### SUMMARY

Because of the great number of men and women of the armed forces who have lived in areas highly endemic for amebiasis and who now have returned to civilian life, amebiasis will probably be more frequently encountered in post-war civilian practice in New England

The clinical picture, laboratory findings, proctoscopic findings and roentgen-ray manifestations in 60 cases of amebiasis are reviewed The diagnosis of amebiasis often requires extensive study, including repeated stool, proctoscopic and x-ray examinations

The liver is not too infrequently involved in amebiasis, and the etiologic agent cannot be demonstrated in a large percentage of cases

The proctoscopic visualization of the rectosigmoid mucosa in chronic amebic dysentery may be indistinguishable from that of idiopathic ulcerative colitis

The similarity of amebic dysentery to functional disturbances, frequently described as "irritable colon," "mucous colitis" and so forth, is discussed Patients presenting such a symptom complex, who have had a previous history of amebic dysentery or have lived in an area highly endemic for *Endamoeba histolytica* should be given a trial of antiamebic therapy

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## ATYPICAL ADDISON'S DISEASE ASSOCIATED WITH DIABETES MELLITUS\*

### Report of a Case

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SINCE the description of the syndrome of adrenal cortical insufficiency by Addison in 1855, a review of the literature reveals only 16 accepted cases in which this syndrome appeared in combination with diabetes mellitus. Nearly seventy-five years elapsed after Addison's paper before a case showing this combination was reported by Unverricht<sup>1</sup> in 1926. It has since been recognized that these cases fall into three distinct groups, depending on the time of development of one disease in relation to the other. Thus, there are 4 cases in which, as nearly as could be determined, the two diseases developed simultaneously, 3 cases in which patients with Addison's disease subsequently developed diabetes mellitus and 9 cases in which Addison's disease followed the onset of diabetes mellitus (Table 1).

The following case, in which the diabetes was present for at least two years before the Addison's disease made itself apparent, is reported not only as an additional case of this rare combination of two metabolic diseases but also because of the markedly atypical character of the picture of adrenal cortical insufficiency as it affected the patient.

K. M., a 20-year-old Irish girl, was first admitted to the hospital on November 1, 1944, in severe diabetic acidosis. The past history was essentially irrelevant until 4 months before admission when she noted the sudden onset of polyuria, polyphagia, polydipsia, weakness and weight loss. A physician made a diagnosis of diabetes mellitus, gave her a dose of insulin and placed her on a restricted carbohydrate diet, with instructions to return in 1 week. Because she felt somewhat better and did not want to stop work, however, she did not return. Five days prior to admission she failed to observe her diet because she felt very hungry. Two days later she developed a sore mouth, nausea, vomiting and dizziness. On the day of admission she was seen by her doctor because of progression of these symptoms. He administered 35 units of protamine-zinc insulin and 30 units of regular insulin and sent her to the hospital.

Physical examination revealed an acutely ill, dehydrated and lethargic young woman whose mouth contained scattered ulcerated lesions involving the gingiva as well as other mucosal areas. The chest was clear and the heart was normal. The skin was dry and warm and somewhat loose. The rest of the physical examination was negative.

The blood pressure was 115/65 and the pulse was of good quality.

The urine showed a + + + + test for sugar, a + + + + test for acetone and a + + test for diacetic acid. The blood sugar was 360 mg. per 100 cc., and the carbon dioxide combining power 32.1 vol. per cent.

A diagnosis of diabetes mellitus and diabetic ketosis was made and the patient was started on treatment with continuous intravenous fluids and insulin. During the following 20 hours she received a total of 390 units of regular insulin and 5660 cc. of 5 per cent glucose in physiologic saline solution at which time the blood sugar had fallen to 130 mg. per 100 cc. and the carbon dioxide combining power had risen to 48 vol. per cent. The urine showed a + test for sugar with no acetone or diacetic acid. By that time the oral condition had become much worse and the temperature

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had risen to 101°F. She was placed on sulfadiazine for 2 days, followed by 4 days of penicillin, with good results. Meanwhile, an attempt was made to regulate the diabetes with the use of protamine-zinc insulin. She was placed on a daily diet of 250 gm of carbohydrate, 90 gm of protein and 80 gm of fat (2080 calories), and on this diet she required 70 units of protamine-zinc insulin to regulate her sufficiently well for discharge. It was on this regime that the patient was referred to the diabetic clinic for further care.

For the next 2 years the patient attended the diabetic clinic but was irregular in her appearances and was consequently difficult to control. At various periods the insulin dosage had varied from 40 to 70 units of protamine-zinc insulin. She had no further episodes of acidosis, but the urine frequently showed a ++++ test for sugar. She admitted dietary excesses and apparently had no insight

the injection the patient became conscious. Shortly thereafter the urine was again tested and again found to be free of sugar and acetone. Because she still appeared somewhat lethargic, another 25 gm of glucose was given intravenously, after which she was taken to the ward, where the urine was again examined and showed a ++++ test for sugar with no acetone. She was quiet and still lethargic but was able to answer questions rationally, after a short delay.

Examination of the blood on the next morning revealed a hemoglobin of 68 per cent and a white-cell count of 7700, with a normal differential. The blood sugar was 215 mg, the cholesterol 215 mg and the urea nitrogen 18 mg per 100 cc. The sedimentation rate was 42 mm (Westergren) in 1 hour.

The temperature was 101°F, and the patient had no specific complaints except for marked weakness and lassitude.

TABLE 1 *Previously Reported Cases of Addison's Disease and Diabetes Mellitus\**

AUTHOR	YEAR REPORTED	SEX	AGE	PATHOLOGICAL DIAGNOSIS
Patients with simultaneous diabetes and Addison's disease				
Arnett <sup>2</sup>	1927	F	39	Atrophy
Levy-Simpson <sup>4</sup>	1932	M	16	Atrophy
Gowen <sup>5</sup>	1932	F	54	Atrophy
Nix <sup>6</sup>	1943	M	39	Atrophy
Patients in whom Addison's disease developed first				
Rhind and Wilson <sup>7</sup>	1941	F	32	Atrophy
Thorn and Clinton <sup>8</sup>	1943	M	23	?
Soffer and Sorkin <sup>9</sup>	1945	M	42	?
Patients in whom diabetes mellitus developed first				
Unverricht <sup>11</sup>	1926	M	32	Tuberculosis
Umber <sup>9</sup>	1928	F	52	Tuberculosis
Rowntree and Snell <sup>10</sup>	1931	M	34	Atrophy
Rowntree and Snell <sup>10</sup>	1931	M	—	Atrophy
Rogoff <sup>11</sup>	1936	M	25	Atrophy?
Bloomfield <sup>12</sup>	1939	M	30	?
McCullagh <sup>13</sup>	1942	M	—	—
Bowen et al <sup>14</sup>	1942	F	76	Tuberculosis
Bickel <sup>15</sup>	1945	M	35	?

\*Modified from Soffer.<sup>9</sup>

whatever into her condition. Three weeks before the second admission she was given 100 units of protamine-zinc insulin, but during the succeeding week she had four episodes of mild hypoglycemic shock on successive mornings. Two weeks before admission she was placed on 25 units of protamine-zinc insulin combined with 50 units of regular insulin each morning and had no further episodes of hypoglycemic shock. She stated, however, that for several mornings she had been feeling weak, dizzy and tired.

On the morning of October 31, 1946, the patient awakened feeling weak, dizzy and nauseated. She was aroused with some difficulty but was unable to eat her breakfast. She was given a glass of orange juice and the regular morning dose of 50 units of regular and 25 units of protamine-zinc insulin. Shortly thereafter she became much more drowsy and lethargic, whereupon her physician was called. Under the impression that this represented impending diabetic coma she was given 30 units of regular insulin, after which she became unconscious and totally unresponsive to stimulation and was immediately sent into the hospital.

Physical examination revealed an acutely ill young woman who was completely unresponsive. The pharynx was slightly inflamed, and the lips were dry, with crusted sores at the corners. The tongue was moist. The eyeballs were normal in consistence. The lungs were clear. The apical impulse could not be felt, but there was no cardiac enlargement to percussion. The heart sounds were of good quality. The pulmonary second sound was greater than the aortic second sound. Sinus tachycardia at a rate of 140 per minute was present. Examination of the abdomen was negative. The skin was cool and dry. There was no pigmentation of the skin or mucous membranes, and there were no dark freckles. The deep reflexes were hypoaactive.

The pulse was small and easily compressible. The blood pressure was 90/54.

When seen in the emergency room the patient seemed to be suffering from insulin shock. This impression was further borne out by a urine examination, which showed no sugar and no acetone. She was then given 50 cc of 50 per cent glucose in distilled water intravenously, without dramatic improvement. This therapy was repeated, and directly after

The blood pressure was 98/60, and physical examination was otherwise entirely negative. She was given no insulin, and the urine was examined at regular intervals. During the latter part of the day she appeared very drowsy but did not sleep. She refused to eat more than small amounts at any of her meals. A blood culture was taken in an attempt to explain the fever, but this was later reported to have been negative. An x-ray film of the chest showed normal lung fields and a small heart.

On the next day, the patient appeared even more drowsy and refused everything by mouth except small sips of water. An afternoon urine specimen showed no sugar but gave a ++++ test for acetone, whereupon she was given 5 per cent glucose in physiologic saline solution alternated with physiologic saline solution parenterally. The urine rapidly became acetone free, and the patient became more alert and responsive. After 1600 cc of fluids had been administered the intravenous drip was discontinued. On November 3 she ate much better, and the fractional urine specimens showed a ++++ test for sugar, on each occasion, with no acetone. The rectal temperature was somewhat lower but still ranged between 99 and 100°F. Physical examination was again essentially negative. She had been placed on a regular diet and on November 4 was started on 10 units of regular insulin each morning. On that day the urine specimens taken at 8 and 11 o'clock showed a +++ test for sugar, with no acetone, and she was given an additional 20 units of regular insulin at 11 30 a.m. At 3 p.m., while in the dentist's chair, she suddenly went into a shock-like state and was taken to the ward, where she was seen by an intern and found to be unresponsive, even to painful stimuli. The pupillary reflexes were active, and the extremities were cold and moist. The pulse was regular at about 80 per minute. Blood was drawn for a sugar determination, which was later reported to be 175 mg per 100 cc, and 25 gm of glucose was injected intravenously. The patient responded rapidly, becoming awake and oriented within a few moments. A urine specimen at that time showed a + test for glucose and no acetone. After this episode she remained apparently quite well for the next four days. On a regular hospital diet with 10 units of regular insulin daily the urine persistently showed a ++ to +++

test for sugar. A repeated sedimentation rate was reported as 61 mm. (Westergren) in 1 hour, and the fasting blood sugar was 195 mg. per 100 cc. The temperature ranged between 99 and 100°F. Agglutination tests for typhoid and Salmonella organisms were reported as negative. On November 8 the patient again felt listless and weak and vomited her breakfast. An intravenous infusion was started, and she received 1200 cc. of 5 per cent glucose in isotonic saline solution. During the infusion the symptoms disappeared, and she felt much better, retaining the noon and evening meals. The urine during the day was acetone-free and gave a +++ to ++++ test for sugar. On the next morning she again awakened feeling listless and nauseated. After she had vomited her breakfast another intravenous infusion was started, 5 per cent glucose in isotonic saline solution being used. This was allowed to run for approximately 36 hours, during which the symptoms disappeared and she was again able to eat well and retain all her meals.

It was apparent that this was not an ordinary case of diabetes mellitus. The blood pressure was persistently obtained at a level of 90/54 or less. At the same time the radial pulses were hardly palpable. These factors, in addition to weakness and gastrointestinal disturbance, suggested the possibility of adrenal cortical insufficiency complicating the diabetes. Further questioning of the patient revealed that for the preceding year she had become more aware of increasing weakness and gradual loss of weight. She stated that prior to the present admission the weight had been 116 pounds. On November 11 the weight was 108 pounds. Another factor suggesting the diagnosis of Addison's disease was the rapid improvement in the lethargy and nausea and vomiting following the intravenous administration of glucose and saline solution. With this diagnosis in mind blood was drawn for serum sodium determination, a plain film of the abdomen was taken, and she was tested with tuberculin. The film did not reveal adrenal calcification and the intradermal tuberculin tests were negative up to a 1:100 dilution. Meanwhile, the patient had been changed from regular insulin to 30 units of protamine-zinc insulin each morning with a subsequent diminution in the urinary sugar excretion and with no untoward effects. The low-grade elevation of temperature persisted, as did the elevated sedimentation rate. X-ray films showed minimal thickening of the lining membrane of the right maxillary sinus.

After discontinuance of the intravenous infusion on November 11 the patient did well. She was ambulatory, ate well and appeared cheerful. The urine specimens continued to show sugar although she was on 30 units of protamine zinc insulin daily. On November 16 she again began to complain of nausea, vomiting, weakness, lethargy and severe abdominal pain limited to the epigastric region, without radiation. A hypodermoclysis of 5 per cent glucose in isotonic saline solution was started, but the symptoms persisted. The urine was free of acetone and gave +++ to ++++ tests for sugar on repeated testing. Physical examination revealed the blood pressure to be 68/50 and the pulse to be extremely weak. The lungs were clear and the abdomen was soft and nontender to palpation with no areas of spasticity. On November 18 the hypodermoclysis was removed and an intravenous infusion of 5 per cent glucose in isotonic saline solution was started. In addition she was given 5 mg. of desoxycorticosterone acetate hypodermically twice daily. The clinical response was rapid and dramatic. By the next morning she was no longer nauseated and felt stronger. She ate small amounts of food and the epigastric pain had disappeared. After 2 days of desoxycorticosterone acetate and intravenous therapy she was asymptomatic, and the blood pressure had risen to 100/60. At that time the blood sodium, as determined from a specimen drawn on November 15 was reported as 120.7 milliequiv. per liter, which appeared to confirm the diagnosis. Because of a lack of pigmentation, however, it was decided to establish the diagnosis more firmly. To this end the patient was treated with 6 gm. of supplementary salt in addition to 4 mg. of desoxycorticosterone acetate daily for a period of 11 days, at the end of which the blood sodium was 139.6 milliequiv. per liter — a value well within the normal range. The hematocrit reading was 29 per cent and the serum chloride was 104 milliequiv. per liter. With these values as a base line the desoxycorticosterone acetate was discontinued, and the patient was given a salt-deprivation test, after the kidney function as determined by the urine concentration test and the phenolsulfonephthalein excretion test, had been shown to be normal. On December 1

she was placed on a diet containing 0.6 gm. of sodium a day. On the 7th day of this diet she began to complain of severe nausea and weakness. She appeared to be exhausted and to have lost weight. On the next day she was much worse and vomited several times. The blood pressure had fallen to 78/50, and it was found that she had lost 6 pounds during the course of the test. The hematocrit reading had risen to 41 per cent. The serum sodium had fallen to 127.6 milliequiv. and the serum chloride to 74.5 milliequiv. per liter. In spite of an intake of only 15 gm. of sodium chloride daily, the

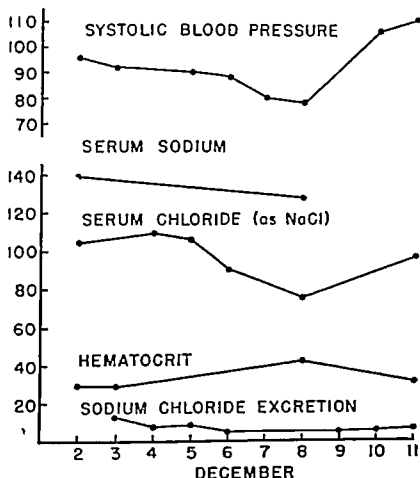


FIGURE 1

daily urinary output of sodium chloride was at no time below 4 gm. These changes are presented graphically in Figure 1.

Treatment with 5 mg. of desoxycorticosterone acetate intramuscularly was immediately started twice daily, with an intravenous infusion of 5 per cent glucose in physiologic saline solution. The response was again dramatic, with rapid disappearance of the symptoms by the next day. The blood pressure rose to 110/55, and the patient began gaining weight, was able to eat and rapidly regained strength and vigor. From then until discharge on December 22, she was symptom free and felt better than she had at any time during the previous year. The protamine-zinc insulin was gradually increased until she was receiving 45 units daily with no deleterious effects and the urine still contained about 10 to 15 per cent of sugar each day. The dosage of desoxycorticosterone acetate was slowly reduced to 1 mg. intramuscularly daily and the supplementary salt intake was maintained at 6 gm. on this routine she was discharged and referred to the diabetic clinic for continued observation.

## Discussion

The salt-deprivation test used in this case was described by Harrop, Weinstein, Soffer and Trescher<sup>14</sup> in 1933. Soffer<sup>2</sup> states that the two findings that make the diagnosis of Addison's disease conclusive are an excess of urinary salt excretion over the intake and a fall in the level of the serum sodium. It was determined to keep the patient on this test diet until she showed some signs or symp-



toms of adrenal cortical insufficiency. She was carefully watched, with frequent determinations of the urinary sodium chloride output, the blood sodium chloride level, the serum sodium and the hematocrit. Blood-pressure readings were made twice daily, and the patient was kept at bed rest. It can be seen that on the basis of sodium chloride intake, it was not until the seventh day that she developed the typical signs and symptoms of adrenal cortical insufficiency.

The absence of pigmentation in this case was a markedly disturbing feature and cast doubt on the diagnosis of Addison's disease until definite proof had been obtained by the salt-deprivation test. Pigmentation is one of the most characteristic features of Addison's disease and is usually the sign that leads one first to suspect this disease. The amount of pigment deposited varies from patient to patient; some patients show only a few black freckles. Others report the appearance of many more freckles than they had previously. Rowntree and Snell<sup>10</sup> found only 1 case of lack of pigmentation in their series of 108 patients with proved Addison's disease.

Another disturbing finding in this case was the fact that the diabetes was only slightly modified by the advent of the Addison's disease. In view of the relation of the adrenal cortex to carbohydrate metabolism, one would expect considerable modification in the diabetes, with a reduction of the hyperglycemia and glycosuria and a lowering of the insulin requirements. Unverricht's<sup>1</sup> case showed a lowering of the amount of insulin required daily from 40 units to 5 units, Rogoff's<sup>11</sup> case a decrease of from 48 to 60 units to 5 to 10 units, Bloomfield's<sup>12</sup> case a decrease from 40 units to 8 units, and Bickel's<sup>15</sup> case a decrease from 50 units to 10 units daily. At the time the patient left the hospital, although she was receiving 45 units of protamine-zinc insulin daily, the urine specimens continued to show a ++ test for sugar, with a daily average excretion of 1 to 1.5 per cent of glucose. The 45 units represents only a slight lowering from the insulin requirements of the preceding two years, which averaged approximately 65 units daily.

In spite of these discrepancies, the diagnosis of Addison's disease appears definitely established on both clinical and laboratory grounds. The poor response to intravenous administration of glucose, given for the insulin shock at the time of admission, should perhaps be considered the first clue that this was not a clear and simple case of diabetes mellitus. Whereas ordinary patients with insulin shock respond rapidly and dramatically to the intravenous administration of glucose, this patient did not and was still somewhat lethargic and disoriented after she had received 75 gm of glucose by vein. This response is in keeping with the course of Addison's disease, since patients with adrenal cortical insufficiency

are markedly sensitive to insulin and go into much deeper shock than ordinary diabetic patients given a similar overdose.

The possibility that this patient was suffering from a combination of diabetes mellitus and Addison's disease dawned on the clinicians when it was realized that the radial pulse was nearly palpable although the general condition was satisfactory. Then the combination of asthenia with a history of weight loss, hypotension and gastrointestinal disturbances manifested by nausea, vomiting and abdominal pain became significant. This, in association with the marked improvement that followed the administration of salt and desoxycorticosterone acetate, suffices to justify the diagnosis. When to this are added the low blood sodium and the typical response to the salt-deprivation test with the fall in the blood chlorides and serum sodium, the lowering of the blood pressure, the rise in the hematocrit and the continued daily loss of more sodium chloride in the urine than was being ingested, it appears that the diagnosis of Addison's disease was definitely established.

#### SUMMARY

A case of atypical Addison's disease associated with diabetes mellitus is reported, and the literature concerning this rare combination is briefly reviewed.

The significance of the salt-deprivation test in combination with the clinical and laboratory findings as evidence for the diagnosis is discussed.  
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## FURTHER OBSERVATIONS ON THE OCCURRENCE OF STREPTOCOCCI OF GROUPS OTHER THAN A IN HUMAN INFECTION\*

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THE occurrence of streptococci of groups other than A is rare in upper respiratory infections such as scarlet fever, tonsillitis and septic sore throat. These streptococci, however, are frequently isolated from sporadic infections, including septic abortion (Harc,<sup>1</sup> 1937), puerperal fever (Fry,<sup>2</sup> 1938), meningitis (Rantz,<sup>3</sup> 1942), urinary infections (Porch,<sup>4</sup> 1941), subacute bacterial endocarditis (Wheeler and Foley,<sup>5</sup> 1945) and miscellaneous conditions (Wheeler and Foley,<sup>6</sup> 1943). The predominant role of Group A streptococci in the over-all pattern of streptococcal disease in man is not disputed. The intention of the present communication is to re-emphasize the potential significance of the streptococci of groups other than A, which are too frequently disregarded by the medical bacteriologist.

During the past two years the serologic groups (Lancefield,<sup>7</sup> 1933) of streptococci isolated in 118 cases of miscellaneous infections occurring in children and adults have been classified. These cases represent but a small percentage of the total patients with streptococcal illnesses admitted to the various institutions from which the data for this study were collected. The sample is selected in that only cases thought likely to be nonrespiratory in origin were included, in view of the difficulties involved in assaying the significance of streptococci of groups other than A isolated from the upper respiratory passages.

Such organisms were isolated in 95 (80 per cent) of this series of 118 cases. Of these 95 strains, a total of 77 (81 per cent) belonged to groups B, C-G, D, E, F and K. Concentrated extracts of the remaining 18 strains, all alpha streptococci, did not precipitate with antisera for groups A-M. Fourteen of these unclassified strains were isolated in cases of subacute bacterial endocarditis.

Streptococci occurred as pure cultures in a total of 93 cases (79 per cent). Of the strains other than Group A, 72 (75 per cent) appeared as pure cultures in primary isolation (Table 1).

The streptococci most frequently encountered in this study were those of Group D. The frequency with which this group was isolated is due in part to the number of cases of urinary infection and the subacute bacterial endocarditis included in the series. However, even if these 34 cases are omitted,

Group D is second only to Group A in frequency of occurrence.

Of the remaining 16 strains of Group D streptococci, 4 were isolated from patients with intra-abdominal abscesses, and 4 from patients with postoperative peritonitis. Group D streptococci occurred as pure cultures in 3 of the former and in 2 of the latter cases. The other 3 strains were isolated in combination with *Escherichia coli*. All 8 patients were adults.

The other 8 strains of Group D streptococci, with the exception of a strain isolated in a case of septic abortion, were recovered from children. It is of interest that in streptococcal septicemia, Group D organisms occurred with about the same frequency as Group A in these cases (Table 1).

Streptococci belonging to groups B, C-G, E, F and K were encountered in infections occurring in adults as well as children. The majority of strains occurred as pure cultures. Groups H, L and M were not encountered in this series.

The streptococci isolated from patients with subacute bacterial endocarditis deserve comment. There were 34 cases in this series. Group D streptococci were isolated from blood cultures in 19 (56 per cent) of these cases, Group K in 1 (3 per cent), and serologically unidentified strains in 14 (41 per cent). Of the last group, 6 strains (18 per cent) synthesized a polysaccharide in 5 per cent sucrose broth but not in 5 per cent raffinose broth, fermented inulin but not raffinose and otherwise seemed to fulfill the criteria for "*Streptococcus s b e*," as described by White<sup>8</sup> (1944), Niven, Kizuta and White<sup>9</sup> (1946) and White and Niven<sup>10</sup> (1946). Of the remaining strains in this group, 5 (14 per cent) seemed to be "*Str. mitis*," and 3 (9 per cent) were "*Str. bovis*." None of the "*Str. bovis*" strains hydrolyzed arginine, and only 1 strain of "*Str. mitis*" attacked this amino acid. This latter strain could be differentiated from "*Str. s b e*" only by its inability to change the viscosity of 5 per cent sucrose broth and its failure to ferment inulin (Table 2).

As observed by Foley and Wheeler<sup>11</sup> in 1945, reaction on horse-blood agar, with the exception of Group A (Lancefield<sup>12</sup>) and Group N (Sherman, Smiley and Niven<sup>13</sup>), does not necessarily correlate with serologic group. Alpha and beta strains were found in groups B and E, whereas alpha and gamma strains were encountered in groups F and K. Strains belonging to Group D exhibited the greatest variation, alpha, beta and gamma reactions were

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observed on primary isolation of streptococci belonging to this group. Also in this group successive strains isolated from the same patients or different colonies in a single primary culture frequently showed variable reactions on horse-blood agar. One strain belonging to Group C-G — streptococci that ordinarily produce soluble hemolysin (Todd,<sup>14</sup>

of cultures cannot be ascertained if only colonies giving a beta reaction on blood agar are studied. This probably accounts for the failure to isolate organisms of groups E, H and K from normal throats during a survey of streptococcus carriers, as reported recently by the Commission on Acute Respiratory Diseases.<sup>15</sup> In the present study, for

TABLE 1 Serologic Classification of 118 Strains of Streptococci Isolated in Cases of Human Infection

SOURCE OF CULTURE	No OF CASES	SEROLOGIC GROUP								UNCLASS- IFIED*	TOTAL INFECTIONS FROM GROUPS OTHER THAN A
		A	B	C-G	D	E	F	K			
Septic wounds	11	6		4	1						5 (45%)
Abscess and peritonitis	17	4	1		8		1	2	1		13 (77%)
Empyema	11	3	1	1	1	1	2	1	1		8 (73%)
Otitis media and mastoiditis	7	5			1			1			2 (29%)
Septicemia	13	4	1	1	3	1		1	2		9 (69%)
Meningitis and brain abscess	6	1	2		1			2			5 (83%)
Septic abortion	3		2		1						3 (100%)
Urinary infection	16		1		15						16 (100%)
Subacute bacterial endocarditis	34				19			1	14		34 (100%)
Totals	118	23 (19%)	8 (7%)	6 (5%)	50 (43%)	2 (2%)	3 (3%)	8 (7%)	18 (15%)		95 (80%)
Strains isolated in pure culture	93 (79%)	21 (92%)	8 (100%)	5 (83%)	32 (64%)	2 (100%)	3 (100%)	7 (88%)	15 (84%)		72 (75%)

\*No precipitation with antisera for groups A-M

1934) — exhibited a gamma variant in primary culture (Table 3)

The etiologic relation of streptococci of groups other than A to disease in human beings admittedly is not so clear-cut as could be desired, since a specific immune response in the host has not yet

example, only 21 (25 per cent) of 82 strains classified into serologic groups other than A gave beta reactions on blood agar

The frequent occurrence of these streptococci in suppurative or generalized infection is in marked contrast to their relatively low incidence in upper respiratory disease. The low carrier rate, together with the further observation that this carrier rate is not subject to the seasonal changes observed in that for Group A streptococci,<sup>17</sup> suggests that the epidemiology of infection due to these organisms is different from that in disease caused by Group A

TABLE 2 Serologic Classifications of 34 Strains of Streptococci Isolated from Patients with Subacute Bacterial Endocarditis

GROUP	NO OF STRAINS	PERCENTAGE
D	19	56
K	1	3
Unclassified	14	41
Str s b e	6	18
Str mitis	5	15
Str bovis	3	9
Total	34	

been demonstrated against them. Such streptococci, except for certain strains of Group C-G, do not produce erythrogenic or soluble toxin (Pomales-Lebrón,<sup>16</sup> 1940), streptolysin or fibrinolysin,<sup>12</sup> as measured by the techniques in use today. However, their isolation, usually in pure culture from suppurative or generalized infection, seems to be indicative of their etiologic significance. Although the results reported here are based on single-colony fishings, except in cases in which the primary culture showed more than one type of colony, it is unlikely that streptococci of groups other than A could occur so frequently as commensals with Group A streptococci of the same blood-agar reaction.

It is evident from the results of the present study and those reported elsewhere<sup>11</sup> that the incidence of streptococci of groups other than A in a given series

TABLE 3 Reaction of Streptococci Isolated in Human Infection on 5 Per Cent Horse-Blood Agar

SEROLOGIC GROUP	NO OF STRAINS			TOTAL
	ALPHA	BETA	GAMMA	
A	0	23	0	23
B	3	5	0	8
C-G*	0	6	1	7†
D	28	9	16	53†
E	1	1	0	2
F	2	0	1	3
K	8	0	1	9†
Unclassified	18	0	0	18
Totals	60 (49%)	44 (36%)	19 (15%)	123

\*All strains trehalose positive.

†Some strains presented more than one type of reaction on primary culture.

streptococci. An epidemiologic grouping, such as that commonly seen in cases of infections due to Group A organisms, is a rare occurrence. The majority of infections caused by streptococci of groups other than A are probably endogenous in origin rather than the result of person-to-person transmissions, the immediate precipitating factor disposing to such infection residing in the host.

rather than the parasite.<sup>18</sup> This is apparent in postoperative infection and in subacute bacterial endocarditis.

The occurrence of the infection with organisms of groups other than A, furthermore, indicates that the "pathogenicity" of the streptococcus is not entirely dependent on serologic characteristics and emphasizes the lack of knowledge concerning the fundamental mechanics of streptococcal infection.

#### SUMMARY

A classification of the streptococci isolated from 118 cases of miscellaneous suppurative or generalized streptococcal infections occurring in children and adults revealed that 95 (80 per cent) of these strains were of groups other than A. Strains belonging to groups D, B, K, C-G, F and E were encountered in that order of frequency, 72 (75 per cent) of these strains occurred as pure cultures on primary isolation. Serologically unclassified alpha streptococci were isolated from this series about as often as Group A strains.

The predominance of Group D streptococci can be accounted for in part by the number of cases of urinary infection and subacute bacterial endocarditis in the series. In 34 cases of the latter, Group D streptococci were isolated in 19 (56 per cent), Group K in 1 (3 per cent) and serologically unclassified alpha strains in 14 (41 per cent). Six of these serologically unclassified strains appeared to be "*Streptococcus s. b. e.*"

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## MEDICAL PROGRESS

### PRACTICAL CONSIDERATIONS OF VENOUS PRESSURE (Concluded)\*

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#### DIAGNOSTIC VALUE OF REGIONAL DIFFERENCES IN VENOUS PRESSURE

In the older literature on venous pressure almost the entire interest centered on values obtained by determination of the venous pressure in one arm. In recent years, it has been demonstrated that comparison of pressure in various peripheral tributaries of the inferior and superior vena cavae greatly increases the diagnostic value of venous-pressure measurements for certain types of disease. Although the literature on the diagnostic significance of regional differences in venous pressure is somewhat limited, the value of this technic is strongly indicated by those who have used it. One can predict that this approach to the use of venous-pressure determinations will find an increasing scope of usefulness. Table 1 presents a list of diagnostic possibilities for a variety of possible regional venous-pressure determinations. Each of these is discussed in further detail in the following sections. Reference is not made to the technic of measurement of intra-atrial pressure by venous catheterization of the right side of the heart.

#### *Diminished Pressure in All Peripheral Veins*

It is well known that in shock (peripheral circulatory failure) the systemic venous pressure is characteristically depressed.<sup>6</sup> Venous-pressure determinations are not ordinarily required for the diagnosis of shock. In fact, the diminished pressure and collapsed state of the veins in this condition frequently make it difficult to insert a needle for venipuncture to obtain blood. Venous pressure in shock may be as low as 10 to 20 mm of water.<sup>48</sup> Gunther<sup>49</sup> and Henstell and Gunther<sup>50</sup> have shown that in cases of shock there is a lowering of intramuscular and venous pressure before the values for plasma volume and arterial blood pressure are altered. When a venous-pressure apparatus is not available one can follow Fishberg's<sup>48</sup> suggestion and note the poor filling of the superficial veins of the upper extremity when the hand is held below the level of the

heart. This clinical observation will suffice to indicate that the venous pressure is low. One would expect the venous pressure to be low in ordinary syncope as well.

Slight temporary depressions in venous-pressure levels may occur normally in a number of procedures. Abdominal compression in the normal supine subject may produce a fall in average arm-vein pressure equivalent to 17 mm of water<sup>2</sup>; normally, the venous pressure falls during the Müller experiment<sup>3</sup>, and hyperventilation produces some fall in venous pressure. Such minor and temporary depressions, which are of no clinical importance, are occasionally noted, and therefore their significance should not be misunderstood.

#### *Elevated Pressure in All Peripheral Veins*

The most extensive use of venous-pressure measurements has been made in the study of congestive heart failure. The literature abounds with reports that attest to the value of the procedure in this connection.<sup>1-7</sup> In the past few years a number of studies<sup>36, 51-58</sup> have led to uncertainty regarding the manner in which elevation of venous pressure results and its place in the mechanism of heart failure. This uncertainty about sequence and mechanism does not detract from the practical value of the test.

In failure of the right ventricle alone and in general cardiac failure there is a comparable elevation of pressure in all the systemic veins. Isolated failure of the left ventricle does not influence the venous pressure.<sup>4, 7</sup> At times, when a patient with right ventricular failure improves rapidly with treatment, disappearance of edema and hepatomegaly may lag behind the return of the venous pressure to a normal level.<sup>3, 4</sup> For example, intravenous administration of certain drugs, including aminophylline, mercurial diuretics and digitalis, is known to bring the elevated venous pressure down rapidly. This may be confusing if earlier measurements have not been obtained. Also, in cases of mild heart failure the venous pressure at rest may be persistently normal.<sup>3</sup> Often, confusion can then be dispelled by careful use of the maneuver for demonstration of the hepatojugular reflux previously mentioned. Cases of persisting right ventricular failure in which determination of venous pressure, including abdominal compression, is entirely normal must be rare. In their recent review

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with inferior-vena-cava blood flow Brams, Katz and Kohn<sup>64</sup> have demonstrated that distention of the abdominal cavity of a dog with air can elevate the iliac venous pressure to a level equivalent to 620 mm of saline solution. Their experiments suggest that artificial pneumoperitoneum in human beings and the so-called "spontaneous valvular pneumoperitoneum,"<sup>65</sup> which results from rupture of an air-containing viscus, could likewise impede blood flow in the inferior vena cava sufficiently to elevate the venous pressure in the leg.

During pregnancy local disturbances in the venous circulation of the lower extremities are quite common, as manifested by the development of varicose veins or the aggravation of varicosities already present, by the appearance of edema in which cardiac, renal, nutritional or endocrine causes are obviously lacking, and by the occurrence of acute thrombophlebitis, usually as a post-partum complication.<sup>66</sup> Studies initiated by Burwell<sup>67</sup> and confirmed by others<sup>66, 68</sup> agree that, although the antecubital venous pressure in normal pregnancy is not significantly different from that in the non-pregnant state, the femoral venous pressure is increased in the latter part of pregnancy. McLennan,<sup>68</sup> in a detailed investigation of 255 pregnant women, made the following observation:

Femoral venous pressure begins to rise in the early part of the second trimester, rises rather rapidly between the twentieth and thirtieth weeks of gestation, then somewhat more slowly to reach an average peak value at term of approximately 240 mm of water. It falls quickly after delivery to nonpregnant levels and apparently lies somewhat below the average control level during the puerperal period of bed rest.

This regional difference in venous pressures is believed to be responsible for the venous collateral patterns that frequently develop during pregnancy.<sup>67</sup> Veal and Hussey<sup>66</sup> regard the elevated femoral venous pressure in pregnant women as contributing to the formation of edema of the lower extremities and the incidence of varicose veins in pregnancy as being directly related to the venous pressure in the legs. The major factor responsible for the elevated leg venous pressure is obstruction to venous outflow by the gravid uterus,<sup>66-68</sup> although Burwell<sup>67</sup> believes that inflow of a large amount of blood via the placenta may be an additional factor.

Nearly all types of malignant renal tumors are capable of invading the renal vein and inferior vena cava<sup>69, 70</sup> and may produce obstruction of the inferior vena cava and even invade the heart. In the older literature obstruction of the inferior vena cava was suspected only when evidence of collateral circulation developed. As may be expected, a striking elevation of leg venous pressure occurs in such cases, and its measurement is warranted in the study of a renal tumor when the question of metastatic spread to the inferior vena cava arises. In a typical case Ferris and Blankenhorn<sup>63</sup> noted a leg venous pressure equivalent to 320 mm of water,

whereas the arm pressure was equivalent to only 70 mm. In a similar manner primary liver carcinoma may invade the inferior vena cava<sup>71</sup> and produce obstruction to blood flow, with resultant increase in femoral-vein pressure.<sup>63</sup> Figures obtained in a representative case revealed a leg venous pressure equivalent to 220 mm and an arm venous pressure equivalent to 50 mm of water.<sup>63</sup>

Ligation of the inferior vena cava as a means of preventing pulmonary embolism in the presence of phlebothrombosis of the leg or pelvic veins has become an accepted therapeutic procedure.<sup>72</sup> One would naturally expect a striking elevation of leg venous pressure in such cases. In a detailed study of 5 patients after ligation of the inferior vena cava Burch and Winsor<sup>73</sup> noted pressures in the veins of the dorsum of the feet ranging from the equivalent of 170 to 506 mm of water, with normal antecubital-vein pressure. The venous pressure in the legs had not returned to normal as long as ten months post-operatively and was inversely related to the degree of development of the collateral circulation. In most cases edema of the feet persisted for many months.

Obstruction of the inferior vena cava from thrombosis, thrombophlebitis, pressure from adjacent masses and primary tumor of the inferior vena cava should act much as ligation of the vessel and should selectively elevate the venous pressure of the legs.<sup>63, 74-76</sup> If the obstruction is of slow onset with involvement of the renal veins the resultant picture is one that closely resembles the nephrotic syndrome.<sup>75</sup> Tumors that metastasize to the inferior vena cava may eventually spread or be carried to the heart and may produce elevation of the venous pressure in the arms as well.

The inferior vena cava passes through the posterior portion of the liver in the right costovertebral sulcus. This close anatomic relation explains the fact that localized intrahepatic tumors may cause inferior-vena-cava obstruction with resultant increase in leg venous pressure. Venous pressures given in a representative case were equivalent to 180 mm of water in the legs and to 40 mm in the arms.<sup>63</sup> A comparable situation could exist for a single congenital cyst or an echinococcus cyst in the right lobe of the liver.

Ferris and Blankenhorn<sup>63</sup> have described a new sign, which is diagnostic of solitary abscess in the right lobe of the liver. In each of 5 consecutive cases of this lesion they noticed an elevation of pressure in the leg vein, that in the arm being normal. The leg pressures in these cases were equivalent to 140 to 370 mm of water, whereas the arm pressures varied from 40 to 80 mm. The leg pressure was noted to drop when pus was aspirated from a liver abscess. The authors postulate that an abscess mass may press not only on the inferior vena cava to raise the leg venous pressure but also on bile or portal radicles to cause obstructive jaundice or

signs of portal congestion. The specific value of the Ferns-Blankenhorn sign becomes clear with the demonstration that diseases causing a more or less symmetrical enlargement of the liver, such as fatty liver, portal cirrhosis, acute hepatitis and diffuse carcinomatosis, do not affect the femoral venous pressure, regardless of the size of the organ. Hepatomegaly due to cardiac failure increases both the leg and the arm venous pressures to a comparable degree. Therefore, a clinical picture characterized by infection, an enlarged liver and increased femoral venous pressure with normal antecubital venous pressure is strongly suggestive of a solitary abscess of the right lobe of the liver.

Subphrenic abscess on the right may also cause a specific elevation in the leg venous pressure.<sup>22</sup> The physical findings in this condition and roentgenologic studies of the chest and diaphragm should make possible its distinction from a solitary liver abscess.

It is well known that thrombosis in the femoral and iliac veins frequently follows certain types of abdominal operations, particularly those in the regions of the large veins. During standard abdominal operations in 10 cases Veal and Hussey<sup>23</sup> studied the effects of operative procedures on the pressures in the antecubital and saphenous veins. It was noted that operative manipulations within the abdominal cavity caused an immediate rise in pressure in the saphenous vein without directly affecting the antecubital pressure. These elevated saphenous-vein pressures fluctuated widely throughout the operation, were occasionally of great magnitude and generally returned to normal at the termination of the operation. In a somewhat similar study Davis, Gilman, and Freedberg<sup>24</sup> noted increases in pressure in the veins of the foot in the course of operations on the uterus and its adnexa, with less striking changes during cholecystectomy and inguinal herniorrhaphy. These authors discussed in some detail the possible role of local venospasm as a factor in the rise in venous pressure obtained in the course of certain operations. It is of interest that Davis et al.<sup>24</sup> observed that the severity and frequency of changes in pressure in the leg veins during abdominal hysterectomy, cholecystectomy and herniorrhaphy had about the same incidence as postoperative thrombosis and embolism in these operations — 4.1 per cent, 2.3 per cent and 1.3 per cent, respectively — as reported by Barker and his associates.<sup>25</sup>

During the postoperative period tight abdominal or groin binders may elevate venous pressure in the legs, particularly if marked abdominal distention develops after the binder is applied.<sup>26</sup>

#### *Elevated Pressure in Arm Veins Alone*

When the superior vena cava is obstructed and the inferior vena cava patent, the pressure in the antecubital veins is significantly higher than that in the femoral vein and shows an additional tempo-

rary increase with the exercise test mentioned above. The same effect may be expected when both innominate veins, both subclavian veins, or both axillary veins are obstructed, although examples of such bilateral venous occlusion must be rare. Katz et al.<sup>20</sup> have reported a case of bilateral innominate-vein thrombosis in which the clinical picture was indistinguishable from superior-vena-cava obstruction except by means of phlebography.

The principal causes of obstruction of the superior vena cava without involvement of the inferior vena cava (superior-vena-cava syndrome) are aneurysm of the arch of the aorta, bronchogenic carcinoma and mediastinal lymphoma.<sup>27, 28</sup> Less frequent causes are metastatic carcinoma of mediastinal lymph nodes, primary thrombosis and mediastinitis.<sup>29, 30, 31</sup>

The completeness, duration and site of the obstruction of the superior vena cava influence the effects noted in the venous circulation. More or less complete obstruction, of course, produces a rather spectacular picture, and most of the reports in the literature are concerned with cases of this type. It has been shown, however, that minor degrees of obstruction also occur and are detectable mainly by venous-pressure measurement.<sup>32, 33, 34</sup> In a study of 35 cases representing the superior-vena-cava syndrome, there were 20 cases in which the venous pressure in the arm was equivalent to 300 mm of saline solution or more.<sup>34</sup> On the other hand, in 6 cases the venous pressure was equivalent to less than 200 mm and could be evaluated only by comparison with measurements of femoral-vein pressure, which were significantly lower. In the same study it was pointed out that there may also be a significant difference of venous pressure in the two arms as a result of involvement of one innominate vein as well as the superior vena cava.

With the passage of time, the venous pressure in the arms may go higher, on account of increasing obstruction to the superior vena cava.<sup>35</sup> Under appropriate circumstances such a change may represent an important indication for surgical exploration of the mediastinum. On the other hand, lowering of the venous pressure has been observed to result from development of collateral circulation, shrinkage of a mediastinal tumor by means of x-ray therapy, relief of complicating heart failure, mediastinal decompression<sup>36</sup> and release of the obstruction of the superior vena cava by severing a constricting band.<sup>37</sup>

The site of obstruction of the superior vena cava is important chiefly with reference to the azygos vein. Obstruction above the point of entrance of this vein into the vena cava has less severe effects for the obvious reason that the azygos then serves as part of the collateral circulation. On the other hand, when this vein is also obstructed, blood from the superior-vena-cava system must return to the heart by way of the inferior vena cava. Under these



circumstances, it has been shown that venous flow and therefore venous pressure, in the tributaries of the superior vena cava, respond to certain maneuvers in a way that resembles the normal response in the tributaries of the inferior vena cava<sup>33, 43</sup>. Thus, the venous pressure in the arms rises when the abdomen is compressed, and a paradoxical oscillation of venous pressure with respiration can be observed in the cervical veins and at times in the antecubital veins as well.

In the superior-vena-cava syndrome the increased volume of blood carried by the inferior vena cava as a collateral channel does not influence the pressure in the femoral veins<sup>43</sup>. It remains normal (low by contrast) unless there is some additional factor obstructing flow in the inferior vena cava.

*Pressure More Elevated in One Arm Than in the Other Combined with Lower or Normal Pressure in Leg Veins*

When there is no cause for localized obstruction to flow in the veins of either upper extremity, it may be expected that venous-pressure measurements obtained simultaneously in both arms will not differ by more than the equivalent of 10 mm of saline solution<sup>24</sup>. This is also found to be true in cases of heart failure, although the measurements, of course, are higher. Conditions that impede blood flow in the innominate, subclavian or axillary vein on one side without equal change on the other produce correspondingly greater differences in venous pressure in the two arms.

In order of frequency, the main local causes of obstruction of the axillary and subclavian veins are malignant neoplasm (usually intrathoracic), thrombosis secondary to heart failure and thrombosis secondary to trauma or effort of the arm and shoulder<sup>84</sup>. The mechanism of venous obstruction by malignant tumors may be compression of the vein, filling of the lumen by invading tumor cells or thrombosis secondary to such invasion. Thrombosis accompanying heart failure has been reported only in severe cases and is thought to be the result mainly of stagnation of venous blood<sup>84</sup>. The fact that it usually occurs on the left side has been explained by the greater immobility of the left arm in most bedridden cardiac patients and by the longer, more tortuous course of the left innominate vein. Traumatic or effort thrombosis has been explained in various ways by different investigators<sup>84, 85</sup>. It is generally believed that the condition results from compression, torsion or stretching of the subclavian or axillary vein on account of effort involving movements of the shoulder. Many kinds of effort have been blamed, Sampson<sup>85</sup> having disclosed eighteen different acts that have been reported to precipitate the condition. At times there is no history of effort or injury. Since most persons are right-handed, effort thrombosis is more frequently seen on the right side.

The causes for obstruction of one innominate vein without corresponding obstruction of the other are the same as those for the superior-vena-cava syndrome<sup>80</sup>. In a report of venous-pressure studies in 27 cases of aneurysm of the aorta and innominate artery, it was found that 85 per cent of cases showed preponderant obstruction of one innominate vein<sup>74</sup>. It was pointed out that the left innominate vein has a more intimate relation to the aortic arch than the right, so that it is not surprising that obstruction on the left side predominates in cases of aortic aneurysm.

When there is obstruction of the veins draining blood from one arm, the difference in venous pressures in the two arms ranges from the equivalent of 20 or 30 mm to the equivalent of 300 mm or more of saline solution<sup>24, 43, 84</sup>. In cases in which obstruction has recently developed, the degree of obstruction can be estimated from the magnitude of the difference in venous pressures, the greater the difference, the severer the obstruction<sup>84</sup>. As a collateral circulation develops, however, the venous pressure on the affected side becomes progressively lower, so that even in cases of complete obstruction of the subclavian vein the pressure may return to the range of normal although not to the level of the unaffected side<sup>84</sup>. In these cases, therefore, the effect of exercise of the hand on venous pressure in the arm is an especially valuable diagnostic adjunct, since the tendency persists for the venous pressure to rise during such exercise on the side of the obstruction<sup>84</sup>.

It has already been mentioned that conditions that alter intrathoracic pressure affect the peripheral venous pressure. In cases of unilateral pulmonary disease without direct involvement of the veins and without attendant change in intrapleural pressure the venous pressure is normal even though the pulmonary lesion is extensive<sup>86</sup>. On the other hand conditions involving one pleural cavity, including pneumothorax, hydrothorax and thoracoplasty, may cause the venous pressure to be higher in the arm on the affected side, presumably because of transmission of increased intrapleural pressure to the innominate vein<sup>87-90</sup>. Less often this type of lesion causes elevation of venous pressure in both arms<sup>88</sup>, and occasionally the effect is noted only in the arm on the unaffected side, possibly because of shifting of the mediastinum with consequent distortion of the venous inflow tracts of the thorax<sup>91</sup>. Usually, the changes in venous pressure that attend pneumothorax and thoracoplasty are transient, subsiding within a few months even though the pneumothorax or thoracoplasty is unchanged<sup>88</sup>. Overholt and Pilcher<sup>89</sup> have emphasized the fact that in their experience unilateral elevation of venous pressure after thoracoplasty is an unfavorable sign and should cause postponement of additional surgery until the measurements are again normal and equal bilaterally.

*Pressure More Elevated in One Foot Than in the Other and Normal in Arms*

Occasionally, circumstances warrant the determination of venous pressure at the ankle under basal conditions. The study of Tyson and Goodlett<sup>22</sup> indicates that when the femoral vein in one leg is acutely occluded by a clot the venous pressure at the same ankle is elevated with the leg at rest. A similar result could be expected when one iliac vein is occluded. Should the ankle pressure be normal and obstruction still suspected, the exercise test described above<sup>23</sup> should be performed.

Pressure determinations in leg veins are particularly indicated for evaluation of cases of edema of the lower extremities. If the venous pressure is normal in the lower legs after the exercise test, it can be assumed that the major venous channels are patent and the cause for the edema should be looked for elsewhere.<sup>24</sup>

In cases of arteriovenous fistula involving the vessels of the lower extremity, the pressure in the veins near the fistula is elevated, but the systemic venous pressure is normal in the absence of cardiac failure.<sup>25</sup> A similar situation is found when the arm is the site of an arteriovenous fistula.

*Dissociation between Pressures in Jugular Vein and General Peripheral Venous System*

It has been demonstrated that venous pressures can be determined accurately and safely in the jugular veins. Myerson and Loman<sup>47</sup> have described the technic for measuring pressure in the internal jugular vein, and Hitzig<sup>48</sup> gives in some detail the procedure of utilizing the external jugular vein for determining pressures. These veins are not generally used except in research studies, the indications for determining the pressure in the internal or external jugular vein being limited. Hitzig<sup>48</sup> has demonstrated that this technic is a much more accurate means of studying inspiratory filling of the cervical veins than clinical inspection and palpation.

Loman and Dameshek<sup>49</sup> have reported a case of polycythemia with elevation of the internal jugular pressure in both veins to the equivalent of 300 mm of water and with a general venous pressure equivalent to only 80 mm. The initial spinal-fluid pressure was equivalent to 380 mm of water. After venesections totaling 3060 cc of blood in twelve days the pressures in the internal jugular veins and spinal fluid were normal. Apparently, the plethora of this disease was responsible for the increased internal jugular pressure. Other causes of dissociation between pressures in the internal jugular vein and peripheral veins are also discussed by the same authors. Thrombosis of a lateral sinus would be expected to cause a low or absent pressure in the corresponding internal jugular vein. Obstruction to a lower part of the jugular vascular channel could readily produce dissociation with an elevated

internal jugular pressure. An obstructing lesion in the neck or upper mediastinum could readily obstruct one or both jugular veins. An obstructive thrombophlebitis of the internal jugular vein may follow septic throat infections.<sup>51</sup>

The pressure in the antecubital vein may be much lower than that in the veins of the neck in persons with the clinical picture of shock due to sudden onset of severe heart failure.<sup>52</sup> Ordinarily, most patients with cardiac failure have a comparable elevation in both the arms and the external jugular veins.

*Elevated Portal-Vein Pressure with Normal Pressure in Arm and Leg Veins*

The portal-vein pressure may be determined at laparotomy by insertion of the needle of the venous-pressure apparatus into an omental vein or the splenic vein after delivery of the spleen and before ligation of any of the larger splenic veins.<sup>53</sup> This technic has proved of value in the study of cases of portal cirrhosis and Banti's syndrome.<sup>57</sup> A comparison of the portal venous pressure with the systemic venous pressure—that is, the arm-vein pressure—is particularly valuable. Bellis<sup>54</sup> found the average normal venous pressure to be 100 mm of saline solution higher than the average pressure in the normal ankle vein, with a range of 140 to 220 mm in contrast to normal ankle pressures of less than 120 mm. In a case of advanced portal cirrhosis with ascites the portal venous pressure was equivalent to 400 mm of saline solution. Thompson et al<sup>55</sup> observed that the splenic-vein pressure ranged from 250 to 500 mm of water in Banti's syndrome with chronic schistosomiasis and from 270 to 470 mm in Banti's syndrome associated with cirrhosis. These figures contrast strikingly with supposedly normal splenic-vein pressures equivalent to 100 to 125 mm of water measured in cases of typical hemolytic jaundice. The arm venous pressures in these cases of Banti's syndrome were essentially normal. It can be concluded that the determination of venous pressures in the splenic vein or in the portal tributary vein is a reasonably accurate although complicated procedure of increasing significance not only in research studies but also in the evaluation of cases for surgical therapy. Blakemore<sup>56</sup> has recently suggested that venous-pressure readings, properly taken at operations designed to shunt the portal blood flow in cases of congestive splenomegaly, are an indispensable aid in localizing the site of obstruction in the portal radicles. The effectiveness of a portocaval shunt in such cases can be shown by determination of the portal pressure before and after the shunt is produced. In 4 cases reported by Blakemore<sup>56</sup> the pressures were equivalent to 310 to 400 mm of water before and 180 to 240 mm after the shunt was produced.

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# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 33481

#### PRESENTATION OF CASE

A forty-six-year-old man entered the hospital because of paroxysmal nocturnal dyspnea.

The patient had enjoyed excellent health until five or six years before admission, when he noted the onset of mild exertional dyspnea. During the three years prior to admission he had occasional frontal headaches. Nine months before admission an overpowering feeling of fatigue and severe exertional dyspnea set in, causing the patient to give up work. He was hospitalized at that time, found to have diabetes and put on a dietary regime with 15 units of insulin a day. Subsequently, he felt improved and returned to work. Five months later he consulted another physician, who stated that he no longer needed insulin and placed him on a vegetable diet. He did not do well. During the month before admission several new symptoms developed: paroxysmal attacks of dyspnea occurring almost nightly, orthopnea requiring two or three pillows, marked ankle edema and precordial pain on effort. The exertional dyspnea became very severe, and he was bothered by frequency and nocturia (five times). A week before admission he had marked anorexia and occasional vomiting. He had lost 60 pounds during the present illness.

The patient had no knowledge of hypertension. There had been no tinnitus, epistaxis or vertigo and no kidney symptoms except gradually increasing frequency during the present illness. The alcoholic intake averaged a pint a day for fifteen to twenty years until eight months before admission, but the food intake had always been good. He admitted that he had had gonorrhea five times and syphilis once about fifteen years before entry. The former was treated with irrigations, and the latter with a styptic pencil.

Physical examination disclosed a well developed and well nourished, slightly dyspneic man sitting up in bed. The fundi showed tortuosity of the vessels, hemorrhages, exudates and blurring of the disks. The neck veins were distended and pulsating.

The heart was markedly enlarged with the apex in the anterior axillary line in the sixth intercostal space. There were a Grade III systolic murmur, heard all over the precordium but best heard at the apex, and a blowing diastolic murmur along the left sternal border. The liver edge was smooth and exquisitely tender and extended four fingerbreadths below the costal margin. The spleen was felt three fingerbreadths below the costal margin and was also tender. No ascites was noted. There was marked pitting edema of the ankles.

The temperature was 98°F, the pulse 80, and the respirations 20. The blood pressure was 240 systolic, 160 diastolic.

Examination of the blood revealed a hemoglobin of 14.4 gm per 100 cc. and a white-cell count of 9100, with 88 per cent neutrophils. The urine showed a +++ test for albumin and a negative test for sugar, and the sediment contained occasional hyaline and granular casts and occasional white cells. A blood Hinton test was negative. The nonprotein nitrogen was 48 mg per 100 cc and a phenol-sulfonephthalein test showed 10 per cent excretion of the dye in two hours.

An x-ray film of the chest disclosed left ventricular enlargement and considerable pulmonary congestion. There was probably some fluid in the left costophrenic angle. An electrocardiogram showed left ventricular strain and auriculoventricular block.

During the hospital stay the patient was at first irritable but later lapsed into coma. A lumbar puncture on the eighth hospital day revealed an initial spinal-fluid pressure equivalent to 425 mm of water. The pressure fell to 275 mm with the removal of 8 cc. The fluid contained 2 red cells per cubic millimeter but no white cells. The protein was 80 mg per 100 cc. The serum nonprotein nitrogen gradually rose, reaching 130 mg per 100 cc terminally, with a carbon dioxide of 20.4 milliequiv per liter. The uric acid was 10.1 mg, the calcium 7.5 mg and the phosphorus 4.6 mg per 100 cc. The blood pressure varied between 260 systolic, 190 diastolic, and 205 systolic, 135 diastolic. The respirations were Cheyne-Stokes in character during almost the entire hospital stay. On the seventh hospital day the temperature suddenly rose from normal levels to 100.8°F and thereafter varied irregularly between 100 and 101°F until the twentieth hospital day, when it gradually started to climb, reaching 105.8°F during the next four days. The pulse rate, from the seventh day on, averaged between 90 and 110, with several brief spikes to 110. The respiratory rate was very irregular, varying from 20 to 30. On the fourteenth and fifteenth days cough was a prominent symptom, and thereafter frequent note was made of rales at the bases. The urine never showed more than a few white cells.

The patient died quietly on the twenty-fourth hospital day.

## DIFFERENTIAL DIAGNOSIS

DR RICHARD J CLARK From this protocol we develop the impression of a definite type of patient. He was a forty-six-year-old man who entered the hospital well nourished, in spite of the fact that he had lost 60 pounds in weight. Evidently he had been obese. He admitted that he had had gonorrhea on five occasions. He gave a history of syphilis, which had been treated with a styptic pencil. He had taken a pint of alcohol daily for twenty years. In spite of this prophylactic medication severe hypertension and severe arterial disease developed. At the outset we may assume by definition that he had malignant hypertension. It is also quite certain that he had congestive heart failure of a severe degree involving both the left and right sides of the heart. In addition, he had severe renal disease and died with a picture of terminal uremia. Perhaps I should stop here and stay out of hot water, but I do find a number of intriguing side issues that are of interest to speculate upon.

In the first place, did the patient have a simple malignant hypertension or possibly a pheochromocytoma? The history mentions glycosuria. We do not know definitely that he had diabetes, although there was at one point sufficient glycosuria to require insulin. At the time of entry to the hospital there was no positive evidence of diabetes. In a patient with hypertension and glycosuria, pheochromocytoma is one of the factors to be considered. Ordinarily, pheochromocytoma is regarded as presenting a paroxysmal type of hypertension, of which there is no definite evidence in the case under discussion. We do know that the diastolic pressure ranged between 135 and 190. Green\* has reported a series of 51 patients with pheochromocytoma. The interesting thing is that only 14 presented definite paroxysmal hypertension. The other 37 had sustained hypertension, and 4 of these ran a course of malignant hypertension with death from cerebral vascular accidents, congestive failure and uremia. Some hypertensive patients upon whom sympathectomy has been performed have revealed unexpected adrenal tumors at operation. Apparently, this patient was too sick to have had an intravenous pyelogram done, although this would have been of interest. I see no definite basis on which to make a diagnosis of pheochromocytoma, but such a finding at post-mortem examination would not surprise me.

What about the urinary tract? The patient had very little or nothing in the way of urinary symptoms until approximately a month before death. He had no previous history to suggest acute glomerulonephritis at any time. He did have diabetes, and we might wonder about intercapillary glomerulosclerosis, but so far as I am aware that

has not been described as an accompaniment of the malignant type of hypertension. The same point may be made regarding infections of the urinary tract. The urinary sediment contained only a few white cells, and at no time did he have any appreciable evidence of true urinary-tract infection. He had gonorrhea five times. The amount of frequency (nocturia of five times) in the last month is in some ways a bit more suggestive to me of an obstruction in the urinary tract than it is of a simple renal lesion. Did he possibly have a stricture, or did he have constriction in the region of the prostate causing back pressure? That is a definite possibility, but the symptoms of hypertension developed a considerable time before the urinary frequency, and I cannot conceive of a hydronephrotic picture giving rise to this situation. All in all, the most probable diagnosis so far as the renal tract is concerned is malignant nephrosclerosis.

What about the cerebral status? One of the differential diagnoses of malignant hypertension with encephalopathy is brain tumor. Could the patient have had a brain tumor? He had a high spinal-fluid protein and eye-ground findings that could have been consistent with tumor. On the other hand he had no localizing symptoms and no severe headache. I can see no reason for making a diagnosis of brain tumor in this case and believe that all the findings, including the spinal-fluid pressure and the spinal-fluid protein, are entirely consistent with malignant hypertension and uremia.

Now we come to the heart, which is one of the stumbling blocks along the line. May we see the x-ray films?

DR STANLEY M WYMAN The heart is markedly enlarged, chiefly toward the left and probably chiefly the left ventricle. The aorta is somewhat tortuous. It can be seen in the lateral view, descending close to the posterior chest wall. There is probably a very small amount of fluid in one of the costophrenic sinuses. The hilar shadows are definitely enlarged. Whether this is entirely vascular or whether there are underlying changes in the lymph nodes or possibly in the stem bronchi, I cannot say. We should have two things to verify this point, fluoroscopy and a heavy exposure film. The picture is consistent with congestion, however.

DR CLARK What would you say about the aorta? Do you consider it dilated? Can you define the areas of dilatation if there are any?

DR WYMAN One cannot make an accurate measurement of the diameter of the aorta, except at the arch, where it does not look dilated.

DR CLARK Do you think, from the x-ray point of view, that you can make a reasonable differential diagnosis between left ventricular enlargement in aortic regurgitation and aortic-valve disease as against left ventricular hypertrophy of hypertensive heart disease?

\*Green, D. M. Pheochromocytoma and chronic hypertension. *JAMA* 131:1260-1265, 1946.

Dr. WYMAN Not by x-ray study alone This is consistent with hypertensive heart disease, but we certainly see the same picture without the enlargement of the hili in aortic regurgitation

Dr. CLARK The heart was obviously very much enlarged There was a loud systolic murmur at the apex, which might have been due to organic mitral regurgitation, but with the degree of enlargement it probably represented functional regurgitation The next item is the diastolic murmur heard clearly along the left sternal border We can say definitely that this patient did not have free aortic regurgitation He had no wide pulse pressure and no drop in diastolic pressure Syphilitic heart disease may be engrafted upon hypertensive heart disease Did this patient have syphilitic aortitis or aortic-valve involvement in addition to the hypertensive heart disease? The blood serologic findings were normal Is the spinal-fluid Wassermann test recorded?

Dr. TRACY B. MALLORY No

Dr. CLARK In cardiovascular syphilis the serologic reaction is positive in 85 per cent or more of cases This man was relatively young, and I believe that if syphilitic aortic regurgitation had been developing, which would have occurred in the early developmental stage, the serologic reaction would have been positive Beyond that, the story of syphilis is quite uncertain Certainly, syphilitic aortic regurgitation could not have accounted for the dyspnea of several years' duration such as this patient had, without being much more full blown than it was I shall therefore discard any diagnosis of syphilitic involvement of the heart.

Could he have had rheumatic heart disease along with hypertensive heart disease? Such a combination is common From the x-ray film, if he had rheumatic heart disease, it must have been primarily aortic-valve disease There was no past history of heart trouble or rheumatism That does not rule out the diagnosis, but on the law of chances I shall let it go by the board

How about pulmonary regurgitation giving rise to the murmur? That is a possibility What about hypertension and hypertensive heart disease as possible causes? The electrocardiogram showed definite left ventricular strain and was consistent with hypertensive heart disease. We know from certain series of cases that aortic regurgitation occurs in conjunction with hypertension in between 25 and 7 per cent of cases, without assuming any other disease of the aortic valve. This apparently arises from dilatation of the aorta and aortic ring If that situation ever occurs, it may well have been present in this case with a considerably dilated heart and a tremendous rise in diastolic blood pressure

I shall hold to my original diagnosis of hypertensive heart disease. In addition, I believe that post mortem examination revealed definite evidence

of coronary-artery disease The patient had precordial pain on exertion during the last year of life, and also in the electrocardiogram he showed delayed auriculoventricular conduction These two factors are reasonable evidence on which to make a diagnosis of coronary disease

There is one more problem in this museum of difficulties — namely, the enlarged liver and spleen If we go back in the history we realize that the patient had been taking alcohol in large doses for twenty years Did he have cirrhosis of the liver in addition to the other troubles? Early cirrhosis may produce a nodular liver such as that described, but I am not aware that cirrhosis of the liver ordinarily causes a tender liver The liver described in this case is consistent with the liver of congestive heart failure, and without any other definite evidence to tie to, I shall consider it as such

The matter of the spleen is not quite so easy The patient had no anemia on entry There was no evidence of any blood dyscrasia and no abnormal adenopathy or anything of that sort to associate the spleen with In a cardiac patient with splenic enlargement, particularly with a tender spleen, the first thing to consider is subacute bacterial endocarditis I have already ruled out the ordinary cardiac lesions upon which subacute bacterial endocarditis is usually engrafted Against subacute bacterial endocarditis was the absence of fever on entry or other corroborative physical findings What about splenic infarction? This is one of the other conditions in heart disease that one must consider as a cause for splenic enlargement, but there was no history to substantiate such an episode There are debates about the occurrence of palpable splenic enlargement from passive congestion Some authors state that it never occurs except occasionally in childhood Others say that it occurs on occasion I shall assume that the splenic enlargement in this case was on the basis of a fairly severe degree of passive congestion

What about the terminal episode? The patient was febrile during the last two weeks in the hospital There was no evidence of increasing urinary-tract infection His exitus was a gradual one, without any sudden episode I believe that he developed a terminal bronchopneumonia

Finally, is there any other single diagnosis that can tie up this myriad of findings and symptoms apart from those that I have mentioned? The only one that I can think of is periarthritis nodosa There are a number of problems that present themselves with this diagnosis Periarthritis ordinarily runs a relatively rapid course and yet may drag out over a considerable period, but I cannot conceive of its continuing for five years There was an acute exacerbation, with the appearance of new symptoms, a month before entry It is possible that periarthritis nodosa set in at that point. Periarthritis is usually a febrile disease throughout,

whereas this patient had fever only terminally. It usually causes a leukocytosis, which was lacking, although examination of the blood revealed 88 per cent neutrophils. He did not show an eosinophilia, but this is by no means essential to the diagnosis. All in all, I consider periarteritis nodosa a remote possibility.

I shall conclude essentially where I started, with the belief that this man had an acute malignant hypertension, possibly based on a pheochromocytoma, associated with malignant nephrosclerosis and uremia, as well as hypertensive and coronary-artery disease with congestive failure.

#### CLINICAL DIAGNOSES

Malignant hypertension  
Uremia

#### DR CLARK'S DIAGNOSES

Malignant hypertension  
Pheochromocytoma?  
Malignant nephrosclerosis  
Hypertensive and coronary-artery disease  
Congestive heart failure  
Terminal bronchopneumonia

#### ANATOMICAL DIAGNOSES

*Nephrosclerosis*  
Hypertrophy of heart  
Multiple pulmonary emboli, with pulmonary infarction  
Chronic passive congestion  
Thrombophlebitis, left leg  
Mural thrombus, right auricle

#### PATHOLOGICAL DISCUSSION

DR MALLORY Post-mortem examination demonstrated a greatly enlarged heart, which weighed 750 gm, with apparently normal valves and an aorta that showed very little atheroma and no suggestion of syphilitic scarring. The coronary arteries contained a few flecks of atheroma but no points of significant narrowing. Nevertheless, the myocardium revealed a few minute, microscopic foci of absorption of muscle cells although no gross infarction. A marked degree of nephrosclerosis was found in the kidneys. From the histologic point of view they did not show any of the stigmas of malignant hypertension. There were no changes in the glomeruli and no necrosis of the walls of the blood vessels. This does not surprise me very much, since I have never been able to make a satisfactory correlation between the so-called "clinical malignant hypertension" and the so-called "pathological malignant hypertension." Usually, the pathological findings are consistent in patients who die in uremia in contrast to those who die in cardiac failure or from cerebral accidents. Since this patient was certainly approaching uremia at the time of death, I am a little surprised that the

findings were not present, but there was no trace of them. The brain was essentially normal. There was no obstruction in the urinary tract.

The surprise of the autopsy was the presence of four massive pulmonary infarcts each in a separate lobe of the lung, and I believe that those were the cause of the terminal fever—at least we found nothing else to explain it. There was evidence that there had been multiple pulmonary emboli, some much older than the ones that caused the infarcts. The liver was enlarged and showed only passive congestion. The spleen weighed 490 gm, which is a marked degree of enlargement for chronic passive congestion, but we found no other explanation for it.

DR CLARK How often do you find enlarged spleens at post-mortem examination from passive congestion and heart disease?

DR MALLORY Almost always, but rarely enough enlargement to make us confident that they were palpable. A few years ago I checked over quite a series of cases of splenomegaly, and unless the spleen weighs 400 gm it is rarely felt. It must be three times the normal size before one begins to feel it. The spleen in this case was distinctly larger than that.

DR CLARK This case emphasizes a point that I should certainly have mentioned in any patient with chronic heart failure in whom one suspects bronchopneumonia, one is probably wrong, it is usually pulmonary infarction.

DR MALLORY Possible sources of the thrombi were the deep veins of the leg and the calf, and also a thrombus in the right auricle of the heart. I cannot say from which source the pulmonary emboli came.

A PHYSICIAN Was any bacteriologic examination done?

DR MALLORY Yes, it was entirely negative.

#### CASE 33482

##### PRESENTATION OF CASE

*First admission* A fifty-six-year-old man with a six-year history of attacks of wheezing and dyspnea was admitted to the hospital during an exacerbation of asthma.

He had had severe cough and wheezing for two weeks, requiring adrenalin two or three times a day. The dyspnea had prevented sleep. The cough had produced about a cupful of yellow sputum a day, but he had had no fever. He admitted exertional dyspnea for four or five years and had been unable to work for two years. He denied any definite allergy. A maternal grandmother had had asthma.

Physical examination showed a cyanotic, obese man with a barrel-shaped chest. Respiration was shallow and almost entirely diaphragmatic. There were coarse "squeaks" over both lung fields. Moist

rales were present bilaterally. The heart sounds were distant, and the blood pressure was 130 systolic, 80 diastolic. The liver edge was palpated 7 cm below the costal margin, the upper border being at the sixth rib. There was moderate pitting edema of the ankles.

Examination of the blood revealed a red-cell count of 4,550,000, with a hemoglobin of 9.7 gm, and a white-cell count of 17,200, with a normal differential. The urine showed a +++ test for albumin and had a specific gravity of 1.016. The sediment contained 30 red cells and 40 white cells per high-power field, as well as granular casts. An electrocardiogram showed a normal rhythm at a rate of 80 to 90, with small Q waves in Leads 1, CF, and CF<sub>4</sub>. A phenolsulfonephthalein test showed 30 per cent excretion of the dye in half an hour and 70 per cent in two hours. The nonprotein nitrogen was 50 mg per 100 cc.

An x-ray film of the chest disclosed scattered areas of fibrosis in both lung fields. The hilar shadows were moderately enlarged, and there was an area of soft mottled density in the middle portions of both lung fields and at the bases. There was a small quantity of fluid in each pleural cavity.

The patient improved slowly with adrenalin, aminophylline, a low-salt diet and sedation. The urinary sediment showed 200 red cells and 12 white cells per high-power field. He was discharged unimproved on the thirteenth hospital day.

*Final admission* (ten months later). The dyspnea and cough, which was productive of about a pint of yellow, sometimes blood-streaked sputum, persisted. Nocturia (four times), developed without other urinary symptoms. Three weeks previously the dyspnea and asthma had increased, and twitching movements of the face and extremities had developed.

Examination revealed an extremely ill, cyanotic man. Numerous coarse rales were audible at the left base. Dullness and diminished breath sounds were present at the right base. There were no cardiac murmurs.

The temperature was 99.6°F, and the respirations were 35 to 40. The blood pressure was 180 systolic, 100 diastolic. The pulse was 110 and regular.

Examination of the blood revealed a hemoglobin of 7.5 gm and a white-cell count of 12,000. The urine gave a ++ test for albumin and had a specific gravity of 1.012, the urinary sediment contained numerous red cells, white cells and casts. The nonprotein nitrogen was 60 to 85 per 100 cc, the blood calcium 7.6 mg, and the phosphorus 17.0 mg. The phosphatase was 5.4 units. An electrocardiogram showed a normal rhythm (100), a PR interval of 0.14 second and a tendency to left-axis deviation. The Q waves were small and the T waves were upright in Leads 1 and 2.

In spite of digitalization, aminophylline, a washed-red-cell transfusion and other supportive measures the patient died in marked respiratory difficulty on the third hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR MYLES P. BAKER. With the facts at hand it seems to me that the house-officer writing a discharge summary at the end of the first admission must have had some doubt regarding just what he had been dealing with in this patient. It is the story of a cyanotic, asthmatic patient who had had attacks of wheezing dyspnea for years and in whom, with a presumptive diagnosis of bronchial asthma, adrenalin had given definite relief. He was later admitted with signs of bronchiectasis and, by description, an emphysematous chest. The question probably came up on admission whether a superimposed bronchial infection was involved or whether there was an element of heart failure, particularly right-sided heart failure, in view of the cyanosis, the apparent enlargement of the liver and the ankle edema. There was a noteworthy absence of hypertension. With further study the electrocardiogram proved to be not that typical of chronic cor pulmonale, with the development of a prominent S wave in Lead 1 and a prominent Q wave in Lead 3, and there were no inverted T waves in the first chest leads. Nor have we certain evidence of cardiac failure. The liver may have been low because of the emphysematous chest. The upper border may have been at the sixth rib. The man was obese, and it is difficult to feel a liver in such a patient who is breathing rapidly. The edema of the ankles may have been due to obesity and local lymphatic obstruction and not to myocardial insufficiency. The finding of evidence in the urinary sediment of a renal lesion is important and is emphasized in this protocol by the statement that on discharge the patient had a persistent and unexplained hematuria. He had renal insufficiency to judge from the one phenolsulfonephthalein test. He had anemia, for which we have no explanation. The leukocytosis may be explained on the basis of bronchiectasis, but that is not definitely established.

The x-ray examination of the chest is important in arriving at a diagnosis. I suggest that Dr Wyman show these films.

DR STANLEY M. WYMAN. The first two sets of films show mottled density in the upper lung fields, particularly on the right. This is essentially unchanged in the two films taken five months apart. There is a suggestion of some mottling in the left midlung field. I cannot be sure of the disease in the lower lung fields, although there is a suggestion in one or both of the lower lobes. The fluid described in the costophrenic sinuses is not impressive. The heart does not appear to be enlarged, it has no characteristic configuration. The aorta is not remarkable. I can see no definite hilar or mediastinal



masses The last film, which was taken five months after the first, shows a marked change The heart now appears to be definitely enlarged, and the enlargement seems to be chiefly left ventricular There is a good amount of fluid in the right pleural space The upper lung fields now show mottled density as on the first examination, with new hazy density in the lower lung fields on both sides, probably in the lower lobes

DR BAKER The picture on admission is not that of a prominent pulmonary conus?

DR WYMAN No, the hilar shadows are prominent, but there is no definite enlargement of the base of the pulmonary artery Along the upper heart borders I cannot see any essential change in the appearance of the hilar shadows in the last observation The main changes have taken place in the lung fields and in the heart size

DR BAKER This patient was not treated with diuretics and apparently not digitalized and was probably discharged with the diagnosis of bronchial asthma and a renal lesion of undetermined nature — that is, probably, some form of nephritis The most significant features about the final admission are the relentless progress of the disease toward the uremic picture with which he entered the hospital, the rising blood nonprotein nitrogen to confirm this impression, the progressive anemia and the appearance for the first time of arterial hypertension

The question of diagnosis seems to me to boil down into one or two possibilities This man may have had bronchial asthma that had been developing in an insidious fashion, in addition to a renal insufficiency that had contributed to his increasing disability of the past few years and ultimately proved fatal, this renal insufficiency being due to one of the usual causes — glomerulonephritis, essential hypertension or pyelonephritis — or to one of the rare causes, such as polycystic kidneys There is another possibility that would account for both bronchial asthma of years' standing and renal failure, namely, periarteritis nodosa

In the few moments that remain we should go a little farther into that possibility About seven or eight years ago Dr Rackemann<sup>1</sup> reported briefly on eight cases with a combination of bronchial asthma and periarteritis nodosa, four of which died and four were living He noted that Dr Greene had reviewed the literature of periarteritis nodosa and found that 8 per cent of patients had asthma, presumably bronchial asthma, although in the discussion of the paper some question was raised whether some of the cases of asthma were cardiac, rather than true allergic cases A few years before 1936 some observers reported 3 cases of apparently "run of the mill" asthmatic patients who became worse, began to run fevers, developed some of the diverse symptoms of periarteritis nodosa, such as cutaneous manifestations and polyneuritis or renal failure, and died<sup>2</sup> In the larger reported series of

cases of periarteritis nodosa there are usually 1 or 2 in which bronchial asthma is either the chief complaint on admission or very prominent in the past history The x-ray picture of the chest in this patient as described in the protocol sounds very much like a few lesions demonstrated by chest x-ray study in cases of periarteritis nodosa I must say that the x-ray findings as Dr Wyman demonstrates them are not what is described in these well studied cases<sup>3</sup> In periarteritis nodosa there is usually a more extensive involvement of the hilar region, and a picture consistent with small pulmonary infarcts rather diffusely distributed through the lower lobes, with small pleural effusions I believe that the development of hypertensive heart disease in the course of a year is important In a report of cases of periarteritis nodosa from Johns Hopkins Hospital this point was stressed, the authors mentioning that 1 or 2 patients had variable blood-pressure levels, at first moderately high, then normal and then rising rapidly toward the end to high levels at the time of death from bronchopneumonia<sup>4</sup> The absence of any hypertension ten months prior to this man's death, at a time when he had diminished renal function and hematuria, otherwise unexplained by a lesion in the lower urinary tract, is much against death from glomerulonephritis

Glomerulonephritis without hypertension, even in very late stages, is rare It may occur during the latent stage This man did not have a latent lesion on first admission to the hospital Even in the absence of some of the more accepted manifestations of periarteritis nodosa, such as peripheral neuritis and coronary insufficiency, I put that disease down as my diagnosis because of the absence of any other good cause for the renal insufficiency and because of the association with chronic bronchial asthma and the rapid progress of the disease and its terminal phase to uremia

DR TRACY B MALLORY Dr Burrage, would you tell us your impression?

DR WALTER S BURRAGE I must confess to being the one who had difficulty in writing the discharge diagnosis at the termination of the first hospital entry There are a few points of interest in addition to what Dr Baker has brought out In the first place this patient had a six-year history of asthma with onset at the age of fifty and with no premonitory symptoms This presumably places him in the so-called "intrinsic group" It was therefore not surprising to find that the intracutaneous tests were negative He was cyanotic from the onset, had clubbed fingers and later developed edema of the ankles The hemoglobin was originally 65 per cent, with a red-cell count of 3,100,000 He never had hypertension during the early stages Fluoroscopy was done on several occasions in an effort to differentiate the role of cardiac failure and pulmonary infection as complications of the asthma These examinations demonstrated a heart of rela-

nely normal size, but later ones in particular showed definitely increased lung markings radiating to the bases, which, with the purulent sputum, suggested the possibility of severe chronic bronchitis or even bronchiectasis.

We discussed periarteritis nodosa, but decided against it. The red cells that were always present in the urine were in favor of it as well as of nephritis, but there were none of the multiple symptoms that these patients often have. We also had difficulty in arriving at a diagnosis but finally decided on chronic nephritis, intrinsic bronchial asthma, severe chronic bronchitis and questionable bronchiectasis.

DR MALLORY Dr Lerman, have you an opinion?

DR JACOB LERMAN I saw the patient on the last admission when he entered in severe congestive failure. He had a long-standing asthma with pulmonary fibrosis and infection. We considered the possibility that the shadow on the right side was consolidation, pneumonia or, more likely, infarction, and discussed the question of vein ligation, but did not carry it out because he was in poor condition. So far as renal disease is concerned, there was the possibility of pyelonephritis. Two urine cultures were reported one contained pyocyanous bacilli, and the other abundant colonies of *Staphylococcus albus*. We were uncertain about blaming the renal picture on chronic pyelonephritis. We considered periarteritis nodosa but decided that this diagnosis was untenable without further evidence. One other possibility as a cause of the uremia occurs to me—that is, amyloid disease resulting from long-standing infection. The patient must have had pulmonary emboli in addition to the pulmonary infection of long standing.

DR BAKER The absence of eosinophilia is worth commenting on. It should be emphasized that it is found in less than 20 per cent of cases of periarteritis nodosa.

#### CLINICAL DIAGNOSES

Bronchial asthma  
Cor pulmonale

Hypertensive and arteriosclerotic heart disease.  
Chronic nephritis

#### DR BAKER'S DIAGNOSIS

Periarteritis nodosa

#### ANATOMICAL DIAGNOSES

Subacute glomerulonephritis  
Pulmonary emphysema  
Bronchiectasis, right upper lobe  
Bronchopneumonia, terminal  
Cardiac hypertrophy  
Arteriosclerosis, generalized, moderate

#### PATHOLOGICAL DISCUSSION

DR MALLORY At autopsy the lungs presented a complicated picture. There was extensive bronchiectasis. There was severe pulmonary emphysema, with patchy fibrosis of the lungs, and in both lower lobes there was a very extensive organizing pneumonia of comparatively short duration—perhaps a few weeks or months, I should estimate.

The next point of interest was the kidneys, which were greatly enlarged, weighing 580 gm. The surfaces were rather pale and dotted with petechial hemorrhages. On microscopical examination there was a typical subacute glomerulonephritis. From the histologic point of view it looked even more acute than subacute. The heart was very markedly hypertrophied, weighed 680 gm. In none of the organs did we find any lesion suggestive of periarteritis nodosa so that subacute glomerulonephritis was probably the chief cause of death.

DR CHARLES L. SHORT Was this cor pulmonale?

DR MALLORY No, in cor pulmonale a diffuse hypertrophy of all chambers, most marked on the left, is observed.

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3. McCall, M., and Pennock, J. W. Periarteritis nodosa: our present knowledge of the disease. *Ann. I. A. M.* 21:628-637, 1944.
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Mr John E Farrell, executive secretary-treasurer, presented a report in which he called attention to the formation of a conference of the officers of the New England State Dental Societies, and suggested that the Council might extend an invitation to meet with this dental group at some future date

Dr Joseph Howard commented on the meeting of the National Physicians Committee held in Chicago in September, which was attended by either medical or dental representatives from each of the forty-eight states. The tone of the conference emphasized the communistic inroads made in the country rather than the socialization of medicine

Mr Farrell reported that the radio program "Doctor's Orders," initiated in Providence in 1944, with the co-sponsorship of the Rhode Island Medical Society, is now to be carried over the Yankee Network in New England. The Council recorded itself as approving the program

After reports from the various state representatives, discussion took place regarding a public-relations conference, and the Council voted unanimously that such a meeting be held in Boston, probably on March 7, 1948

Dr John F Conlin, director of medical information and education of the Massachusetts Medical Society, then described the antivivisection situation in New England, and Dr Robert Fleming, chief of the Out-Patient Clinic for Alcoholism at the Peter Bent Brigham Hospital, spoke on "An Out-Patient Approach to the Treatment of Alcoholism"

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## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### REACTIONS TO ANTIRABIC VACCINE

Physicians have so many prophylactic and therapeutic agents for which they are continually having to weigh indications against contraindications that it is most difficult to keep currently informed regarding agents that are used only on rare occasions

Some physicians lose sight of the fact that extremely careful evaluation should be made of every situation in which it appears that the administration of antirabic vaccine is indicated to a person bitten by a dog. Within ten months, there have been 2 fatal cases following the administration of antirabic vaccine in the Commonwealth. These incidents emphasize the fact that all indications and contraindications should be weighed before antirabic vaccine is given. There is a very real danger in the administration of this vaccine. Some kind of reaction usually occurs in about 1 case in 500, and death results in about 1 case in 25,000

In recent months, letters from the Department recommending treatment of persons bitten by dogs

have carried a stamp calling attention to the low prevalence of rabies and suggesting that the vaccine can be withheld in many cases in which it was formerly considered mandatory. Beginning early in September, this stamp was no longer placed on the letters going into Berkshire County because rabies is apparently prevalent among wild animals in New York State along the western border of Massachusetts. A rabid fox has also been found just inside the western border of Connecticut

During the last three years rabies has been an increasing problem in a band of states including New York, Pennsylvania, Maryland and Virginia, as well as in the District of Columbia. During 1943, 1944 and 1945, a total of 5604 rabid animals were found in these states, compared to 1026 in the years 1940, 1941 and 1942. In New York State alone the increase was from 474 cases to 1202

By widespread immunization of dogs with antirabic vaccine, the disease in dogs has been materially reduced, but the wild animals of the State of New York have become infected, particularly foxes and skunks. These animals have been biting domestic animals so that many herd owners have found it necessary to immunize their cattle against rabies

The situation in New England has been much more satisfactory. During the three years, 1940, 1941 and 1942, the number of rabid animals discovered in New England was 222, compared to only 10 during the years 1943, 1944 and 1945. Endemic rabies has apparently been absent from Massachusetts for over two years, and it is believed that wide use of antirabic vaccine among dogs has been largely responsible for reducing the disease from the high level of 1930

It cannot be too strongly emphasized that rabies vaccine should never be given to human beings unless it is strongly indicated. Physicians who are in doubt regarding a particular case will do well to call the Division of Communicable Diseases of the Massachusetts Department of Public Health for current information and recommendations

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## NOTICES

### NEW ENGLAND DERMATOLOGICAL SOCIETY

A regular meeting of the New England Dermatological Society will be held at the Boston City Hospital on Wednesday, December 3, at 2 p m. This meeting is open to members and invited guests

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### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, December 4, at 7 15 p m in the classroom of the Nurses' Residence. The subject "Meconium Ileus" will be discussed. Dr Gertrude Cone will be chairman

(Notices continued on page xviii)

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## LATENT RHEUMATIC MYOCARDITIS\*

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BOSTON

**R**HEUMATIC fever, a systemic disease affecting chiefly the heart, has always been considered to be primarily a disorder of childhood with a markedly diminished incidence of initial and recurrent attacks after puberty.<sup>1,2</sup> At the younger age levels rheumatic fever follows a variable but usually recognizable pattern, with carditis, arthralgia, chorea and subcutaneous nodules as major manifestations and with fever, abdominal pains, skin rashes, epistaxis and changes in the electrocardiogram, sedimentation rate and white-cell count as minor manifestations of the disease.<sup>3</sup>

It is also appreciated, however, that all these features may be absent in any individual case and that characteristic signs of rheumatic valvular disease may be found in persons from whom no previous history of rheumatic fever can be elicited. In children, the only manifestation of recurrent acute rheumatic carditis is frequently the insidious onset of right-sided cardiac failure, the nature of which has been described by Walsh and Sprague.<sup>4</sup>

Less well known, however, is the fact that initial as well as recurrent acute attacks of rheumatic carditis occur in the later years of life, and at these age levels they may arise in the complete absence of characteristic clinical signs, progressing insidiously into acute cardiac decompensation and death.

It is therefore not uncommon for the activity of these processes — more specifically, the myocarditis component — to be completely unsuspected during the life of older patients. Usually, these cases are considered to be instances of cardiac decompensation arising out of the mechanical impairment of the normal valvular function incurred in earlier attacks of rheumatic carditis.

Many reasons exist for the frequency of acute rheumatic myocarditis as a clinically unsuspected

entity in older age groups, the most important of which, perhaps, is the lack of widespread appreciation of the significance of acute rheumatic myocarditis as a fundamental cause of cardiac decompensation in the rheumatic state. Although the point is still a moot one, a number of authors<sup>5-7</sup> agree that the factor precipitating cardiac failure in patients with old rheumatic heart disease is often a reactivation of the rheumatic myocarditis. Rothchild, Kugel and Gross,<sup>8</sup> who have directed attention to this point, make the following observation: "While the causal relationship of active myocarditis to circulatory failure is very striking in the first two decades of life, it is not sufficiently appreciated that in cases of rheumatic heart disease in adults of the third, fourth and fifth decades of life a recurrent rheumatic myocarditis rather than the healed mechanical defects may in the majority of instances be the precipitating cause of circulatory failure." They also point out that a number of patients who have had rheumatic heart disease that has become completely quiescent reach the fifth, sixth, seventh and even the eighth decades of life and ultimately die of a totally unrelated disease without any evidence during life of myocardial failure directly attributable to the mechanical defects of old rheumatic infection.

Another reason for the failure to recognize acute rheumatic myocarditis as a clinical entity in adults is the comparative infrequency with which active rheumatic carditis produces decompensation compared to hypertension, arteriosclerosis and inactive rheumatic heart disease. Only an acute awareness of its possible occurrence will permit its recognition. Finally, in many cases, the disease is completely asymptomatic, and no diagnosis is possible short of anatomic investigation of the heart.

Attention having been directed to several cases of active rheumatic carditis in which the correct diagnosis was not made clinically, a study was made of all the cases of acute rheumatic myocarditis coming to autopsy at the Mallory Institute of Pathology of the Boston City Hospital from 1933 to 1946

\*Presented at a meeting of the New England Heart Association, Boston, January 27, 1947.  
From the First and Third Medical Services and the Mallory Institute of Pathology, Boston City Hospital.

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Specifically, it was desired to determine how often patients with known rheumatic heart disease considered to be inactive clinically are found to have active cardiac disease at autopsy, how often acute rheumatic fever occurs as a true latent disease — that is, in the absence of the usual clinical mani-

### SELECTION OF CASES

The microscopical sections in all cases listed as active rheumatic myocarditis at the Mallory Institute of Pathology in the thirteen-year period from 1933 to 1946, together with the autopsy protocols, were reviewed to obtain a series of proved cases of

TABLE 1 *Cases Diagnosed Clinically as Active Rheumatic Heart Disease Confirmed by Autopsy (Group I)*

PATIENT	SEX	AGE	PREVIOUS ATTACK	PREVIOUS CARDIAC FAILURE	INFECTION	JOINT MANI- FESTATIONS	PHYSICAL FINDINGS			
							PERI- CARDITIS	MURMURS	CONGESTIVE FAILURE	HIGHEST TEMPERATURE °F
M A	M	16	0	0	Sore throat	Poly- arthritis	+	Aortic systolic	+	103.4
A P	M	53	1	0	Upper respira- tory infection	Pains	+	Aortic systolic, aortic diastolic and mitral diastolic	+	100.0
R R	M	2	0	0	Sore throat	Pains	+	Aortic systolic mitral systolic and mitral diastolic	+	103.0
M S	F	13	1	0	Unknown	0	+	Mitral systolic and mitral diastolic	+	104.0
A H	F	7	0	0	Upper respira- tory infection, scarlet fever	Poly- arthritis	+	Mitral systolic and mitral diastolic	+	102.0
R W	M	7	0	0	Sore throat	Shoulder pain	+	Mitral systolic	+	103.0
L N	M	50	3	0	Sore throat	Poly- articular arthritis	0	Aortic systolic, aortic diastolic, mitral systolic and mitral diastolic	0	101.6
W W	M	14	2	0	Upper respira- tory infection sore throat	Pains	+	Mitral systolic and mitral diastolic	+	103.0
J N	M	6	1	0	Broncho- pneumonia	0	+	Aortic diastolic mitral systolic and mitral diastolic	+	104.0
G C	M	9	1	0	—	Pains	+	Mitral systolic and mitral diastolic	+	102.0
J S	M	14	1	0	Upper respira- tory infection	0	0	Aortic systolic aortic diastolic, mitral systolic and mitral diastolic	+	103.0
T C	M	15	—	0	—	0	+	Aortic systolic, aortic diastolic, mitral systolic and mitral diastolic	+	103.0
B R	M	15	Several	0	Upper respira- tory infection	0	0	Aortic systolic aortic diastolic, mitral systolic and mitral diastolic	+	101.0
J A	M	14	Several	0	Sore throat	Poly- arthritis	0	Aortic systolic, aortic diastolic, mitral systolic and mitral diastolic	+	103.0
S D	M	49	1	0	None	Poly- arthritis	0	Aortic systolic aortic diastolic, mitral systolic and mitral diastolic	+	102.0
B M	M	15	0	0	None	Poly- arthritis	0	Mitral systolic and mitral diastolic	+	101.0
K K.	F	13	Chorea	0	Sore throat	Poly- arthritis	+	Aortic systolic, mitral systolic and mitral diastolic	0	102.0
B O	F	4	0	0	Scarlet fever, measles	Poly- arthritis	+	Systolic over pre- cordium and mitral systolic	+	103.0
T S	M	30	1	+	Upper respira- tory infection, sore throat.	Pains	+	Aortic systolic, aortic diastolic, mitral systolic and mitral diastolic	+	100.0
	F	5	0	0	Scarlet fever	Poly- arthritis	0	Mitral systolic and mitral diastolic	+	105.0

f activity, what factors, in retrospect, contributed to a more accurate diagnostic rheumatic disease, and how frequent rheumatic myocarditis occurs without associated rheumatic valvular or peri-

active rheumatic myocarditis. Cases of superimposed acute or subacute bacterial endocarditis were eliminated because of the possibility that the Aschoff bodies were related to the endocardial bacterial infection.<sup>8, 9</sup> Forty-one cases were demonstrated to have characteristic Aschoff bodies in the

myocardium and were available for study. On review of the clinical records, it became apparent that cases of rheumatic myocarditis could be divided into four groups.

Group I comprised 20 cases in which the clinical and pathological diagnoses of active rheumatic fever

post-mortem examination were found to have active rheumatic myocarditis as evidenced by the presence of Aschoff bodies in the myocardium, in addition to the characteristic rheumatic valvular deformity.

Group III included 7 cases in which no diagnosis of rheumatic heart disease, active or inactive, was

TABLE 1 (Continued)

PATIENT	LABORATORY FINDINGS				AUTOPSY FINDINGS		PRINCIPAL ANATOMIC DIAGNOSIS
	SEDIMENTATION RATE	WHITE-CELL COUNT $\times 10^4$	PR. INTERVAL	PERI-CARDITIS	MYOCARDIAL ASCHOFF BODIES	VALV. LESIONS	
M. A.	Normal	23-38	Upper limit of normal	Fibrinous	Acute cellular	Acute mitral and aortic	Pneumonia, lobular, rheumatic heart disease acute decompensated
A. P.	—	18	Upper limit of normal	Fibrinous	Acute cellular	Acute mitral	Rheumatic heart disease acute, decompensated
R. R.	—	20	—	Serous	Acute cellular	Old healed mitral	Rheumatic heart disease old and acute decompensated
M. S.	—	18-32	Normal	Fibro-fibrinous	Acute cellular	Healed mitral and aortic with superimposed acute mitral	Rheumatic heart disease old and acute decompensated
A. H.	+	12-25	—	Sero-fibrinous	Acute cellular	Old mitral	Rheumatic heart disease, old and acute decompensated
R. W.	Normal to +++	11-16	Prolonged	Slight fibrinous	? Early	Old mitral	Rheumatic heart disease old and acute, decompensated
L. N.	—	15-16	Complete block	—	Acute cellular	Healed and recurrent acute mitral	Bronchopneumonia; rheumatic heart disease old and acute decompensated
W. W.	++ to +++	17	—	—	Acute cellular	Healed with recurrent, acute mitral	Rheumatic heart disease old and acute decompensated
J. N.	—	10-42	—	Fibro-fibrinous	Acute cellular	Acute mitral	Rheumatic heart disease acute decompensated
G. C.	—	—	—	Fibrinous	Acute cellular	Healed mitral and aortic with recurrent acute mitral	Rheumatic heart disease old and acute decompensated
J. S.	+	9-11	Prolonged	Fibrinous	Acute cellular	Healed mitral and aortic, with recurrent acute mitral	Rheumatic heart disease old and acute decompensated
T. C.	+++	17-25	Upper limit of normal	Sero-fibrinous	Acute cellular	Acute mitral	Rheumatic heart disease acute, decompensated
B. R.	Normal	19	Typical of auricular fibrillation	Fibrous obliterative	Acute cellular	Healed mitral aortic and tricuspid	Rheumatic heart disease old and acute decompensated pulmonary tuberculosis, minimal
J. A.	Normal to ++	12	Upper limit of normal	Fibrous obliterative	Acute cellular	Healed mitral and aortic	Rheumatic heart disease old and acute decompensated
S. D.	—	14	Prolonged	Sero-fibrinous	Acute cellular	Healed recurrent acute mitral and aortic	Rheumatic heart disease old and acute decompensated
B. M.	Normal to ++	18-19	—	Fibro-fibrinous	Acute cellular	Healed mitral	Bronchopneumonia rheumatic heart disease old and acute decompensated
K. K.	++	15-23	—	Fibrinous	Acute cellular	Healed recurrent acute mitral	Rheumatic heart disease old and acute decompensated
B. O.	—	9-18	Prolonged	Fibro-fibrinous	Acute cellular	Healed recurrent acute mitral	Rheumatic heart disease old and acute decompensated
T. S.	++	5-18	Prolonged	Serous	Acellular ? healing	Healed mitral aortic and tricuspid, with mitral	Rheumatic heart disease old and acute decompensated
L. E.	—	12-18	—	—	Acute cellular	Acute mitral and aortic	Rheumatic heart disease acute decompensated

were in agreement. These cases represent the active clinical process in an obviously recognizable form and are included as a basis for comparison with the following groups.

Group II was composed of 10 cases that clinically were labeled inactive rheumatic heart disease but at

made from the history, physical examination or clinical course but in which autopsy showed both myocarditis and characteristic rheumatic valvular deformity.

Group IV was made up of 4 cases in which no diagnosis of rheumatic heart disease was observed.

during life but in which post-mortem examination revealed acute rheumatic myocarditis without any associated valvular deformity or pericardial involvement

### CLINICAL AND POST-MORTEM DATA

The average age of the 41 cases was thirty-three years, with a range from two to sixty-three years. Only 3 patients were Negroes. There were 25 male

involvement, manifested either by the presence of a friction rub or by actual pericardial effusion. Although not recorded in Table 1, a forceful heaving cardiac apical impulse was common. All but 2 patients had congestive failure, and all had fever. Elevated sedimentation rates were found in all but 2 of the 11 cases in which the test was performed. White-cell counts were consistently elevated, and electrocardiograms taken on 12 patients showed

TABLE 2 Cases Diagnosed Clinically as Inactive Rheumatic Heart Disease but Found to be Active at Autopsy (Group II)

PATIENT	SEX	AGE	PREVIOUS ATTACK	PREVIOUS CARDIAC FAILURE	INFECTION	JOINT MANI- FESTATIONS	PHYSICAL FINDINGS			
							PLRI CARDITIS	MURMURS	CONGESTIVE FAILURE	HIGHEST TEMPERATURE °F
J M	M	36	3	Several	Upper respira- tory infection	No pains for 6 years	0	Aortic systolic aortic diastolic mitral systolic and mitral diastolic	+	98.6
J C	M	28	1	0	0	Pains since age of 12 swollen ten- der ankles	0 ? rub	Aortic systolic aortic diastolic, mitral systolic and mitral diastolic	+	104.0
A R	F	49	5	Several	0	No pains for 1½ years	0	Aortic systolic aortic diastolic, mitral systolic and mitral diastolic	+	101.0
J D	M	54	1	Several	0	None	0	Aortic systolic mitral systolic and mitral diastolic	+	98.6
M P	F	38	2	1	0	None	0	Aortic systolic mitral systolic and mitral diastolic	+	98.6
A C	F	39	0	0	0	None	0	Mitral systolic and mitral diastolic	+	103.0
C M	M	12	3	0	Upper respira- tory infection	Pains in elbows	0	Aortic diastolic mitral systolic and mitral diastolic	+	104.0
E B	F	42	1	0	0	None	0	Aortic systolic aortic diastolic mitral systolic and mitral diastolic	+	99.0
M S	F	45	1	0	Upper respira- tory infections	Pains	0	Aortic systolic aortic diastolic mitral systolic and mitral diastolic	+	106.0 (terminal)
J L	M	63	1	1	0	Joint pains	0	Aortic systolic mitral systolic and mitral diastolic	+	102.0

and 16 female patients. Each of the four groups is considered individually below.

#### Group I

In Group I the average age was eighteen years, with a range from two to fifty-three years (Table 1). It is significant that only 5 patients were over fifteen years of age.

Eleven patients had had at least one previous episode of rheumatic fever. Sore throat, upper respiratory infection or scarlet fever preceding the rheumatic episode was a prominent feature, being present in 14 cases. Two patients had had no preceding infection, and in 3 cases the record did not indicate whether or not there had been a previous infection. Joint pains or actual polyarthritides was prominent, being found in all but 5 cases. Four patients complained of abdominal pain. Thirteen patients had presented evidence of pericardial in-

volvement, manifested either by the presence of a friction rub or by actual pericardial effusion. Although not recorded in Table 1, a forceful heaving cardiac apical impulse was common. All but 2 patients had congestive failure, and all had fever. Elevated sedimentation rates were found in all but 2 of the 11 cases in which the test was performed. White-cell counts were consistently elevated, and electrocardiograms taken on 12 patients showed

PR intervals in the upper limits of normal in 4 and prolonged in 5. In short, the clinical evidence was sufficient to permit recognition of rheumatic activity. At autopsy all the hearts of the patients in Group I, in addition to active myocarditis, showed either old healed rheumatic valvular deformities or acute rheumatic endocarditis, or both. In 8 cases an acute valvulitis was superimposed on an earlier healed process. In every case there was definite anatomic evidence of cardiac decompensation, which was considered to be the cause of death in all but 1.

#### Group II

In Group II the average age was forty-one years, with a range from twelve to sixty-three years (Table 2). It is significant to note that on the average these patients were twenty-three years

older than those in Group I. Previous episodes of rheumatic fever were noted in all but 2 cases in Group II. Five patients had had episodes of congestive failure. In contrast to the frequency of sore throats or upper respiratory infection in Group I, only 3 cases in this group presented evidence of such preceding infections. Joint phenomena were also less striking, only 3 of the 10 patients complaining of recent joint pains. One patient had

From the pathological point of view autopsy demonstrated the classic lesions of rheumatic heart disease in all cases. In addition to the active myocarditis, all the hearts presented typical healed aortic or mitral valvulitis, or both, with stenosis. In 2 cases with old healed valvular deformities a superimposed recurrent acute rheumatic endocarditis was demonstrated by pinpoint fibrinous vegetations along the free margins of the mitral valve. In 9

TABLE 2 (Continued)

PATIENT	LABORATORY FINDINGS				AUTOPSY FINDINGS		PRINCIPAL ANATOMICAL DIAGNOSIS
	SEDIMENTATION RATE	WHITE-CELL COUNT X 10 <sup>9</sup>	PR INTERVAL	PERICARDITIS	MYOCARDIAL ANGIOCYTES	VALVULITIS	
J. K.	—	6	Normal	Fibrous obliterative	Acute cellular	Healed aortic	Rheumatic heart disease decompensated; syphilitic aortitis
J. C.	+	7-30	Prolonged	No	Acute cellular	Healed mitral and aortic	Rheumatic heart disease old and recurrent; acute, decompensated infectious polyneuritis
A. R.	—	8-10	Prolonged	Sero-fibrinous	Acute cellular	Healed mitral and aortic	Rheumatic heart disease old and recurrent acute, decompensated
J. D.	—	—	—	Fibrinous	Acellular	Healed mitral and aortic	Rheumatic heart disease old and recurrent, acute decompensated
M. P.	Normal	12-18	Typical of auricular fibrillation	None	Acute cellular	Healed mitral	Cerebral hemorrhage, pulmonary embolus rheumatic heart disease decompensated
A. C.	Normal +	7-32	Normal	None	Acute cellular	Healed mitral and aortic	Rheumatic heart disease old and recurrent, acute decompensated; pulmonary embolus, small
C. M.	+++	9-18	—	Fibrous obliterative	Acute cellular	Healed with recurrent acute mitral	Rheumatic heart disease old and recurrent acute, decompensated
E. B.	—	15-17	Typical of auricular fibrillation	None	Acute cellular	Healed mitral and aortic	Rheumatic heart disease old and acute, decompensated
M. S.	—	8-11	Typical of complete block	Fibrous obliterative	Acute cellular	Healed mitral	Rheumatic heart disease old and acute, decompensated
J. L.	—	8-14	Typical of auricular fibrillation	Fibrous focal	Acute cellular	Healed and acute mitral and aortic; healed tricuspid.	Rheumatic heart disease old and acute, decompensated

complained of pains for the previous twelve years. Two patients had had no joint pains for several months, and in the remaining 4 cases joint pains were not mentioned. Typical polyarthritis was not observed in any of these cases. Signs of pericarditis, which were common in Group I, were absent in Group II except in a case in which there was a question of a friction rub. All the patients in this group had murmurs characteristic of valvular damage, and all had congestive failure. The temperatures were normal in 4 cases, and in only 4 cases was there rise to over 101°F. Sedimentation rates were determined in only 4 cases and were elevated in 3. The white-cell counts were in general lower than those in the group clinically diagnosed as active. Electrocardiograms were recorded in 8 cases. The PR interval was prolonged in 2 and normal in 2 cases. Three patients were fibrillating, and 1 had complete block.

patients the death was attributable to the decompensated rheumatic carditis. The remaining patient died of a cerebrovascular accident with signs of cardiac decompensation at autopsy.

### Group III

The average age of the patients in Group III was fifty-five years, with a range of twenty-nine to sixty-three — an average of seventeen years older than the patients in Group II and thirty-seven years older than those in Group I. All but 2 patients in Group III were over fifty-nine years of age. The histories had no significant points in common, and such factors as sore throat and joint phenomena were not present except in 1 case (Table 3). Pericarditis was absent in 6 cases. In only 1 case was there any cardiac murmur suggestive of rheumatic disease. Three patients had given clinical evidence of congestive failure, which was attributed in



TABLE 3 Cases of Acute Rheumatic Carditis with Myocardial and Valvular Involvement Not Diagnosed Clinically as Rheumatic Heart Disease (Group III)

PATIENT	SEX	AGE	HISTORY	PHYSICAL FINDINGS			LABORATORY FINDINGS			CLINICAL DIAGNOSIS		AUTOPSY FINDINGS		PRINCIPAL ANATOMIC DIAGNOSIS
				PERI-CARDITIS	MURMURS	CONGESTIVE FAILURE	HIGHEST TEMPERATURE °F	WHITE-CELL COUNT $\times 10^3$	P.R. INTERVAL			PERI-CARDITIS	MYOCARDIAL ASCHOFF BODIES	VALVULITIS
V B	F	59	Weakness, mental changes and coma	0	Aortic systolic and aortic diastolic	+	102 0	18	—	Hypertension + cerebral hemorrhage	Slight serous effusion	Acute cellular	Healed, with superimposed acute mitral	Rheumatic heart disease, old and acute, decompensated
A C	M	63	Pain and tenderness, left calf	0	? Mitral diastolic	+	102 0	4-16	—	Thrombophlebitis, lobar pneumonia, congestive failure	None	Acellular	Healed, with superimposed acute mitral	Massive pulmonary emboli (source, leg veins), rheumatic heart disease, decompensated
J I	M	63	Sudden onset of abdominal pain	0	Aortic systolic	+	99 5	24-27	—	Mesenteric thrombosis, arterio-sclerotic heart disease	Fibrous obliterative	Acellular	Healed mitral and aortic	Mesenteric thrombosis
E B	F	29	Known hypertension with intermittent coma for 10 days prior to admission	0	0	0	100 6	10	—	Subarachnoid hemorrhage, hypertension	None	Rare cellular	Healed mitral and aortic	Rheumatic heart disease old and acute, decompensated
D G	F	60	Operative diagnosis of carcinoma of gall bladder 6 months prior to admission	0	Mitral systolic	0	104 0	9-10	—	Carcinomatosis avitaminosis	Focal fibrous	Atypical cellular	Healed mitral	Carcinoma of gall bladder, with biliary tract obstruction
R. H	F	47	Malaise, chest pain, cough, nausea, fever and joint pains for 2 years	+	Systolic, 3rd left inter-space	0	101 2	22-60	Prolonged	Bronchopneumonia, adhesive pericarditis	Sero-fibrinous	Acute cellular	Acute fibrous aortic	No anatomic cause of death
F B	M	61	Cough, hemoptysis following upper respiratory infection	0	Mitral systolic	0	101 0	—	—	Pulmonary tuberculosis	Focal fibrous	Early acute	Acute mitral	Pulmonary tuberculous

TABLE 4 Cases with Acute Myocarditis, Rheumatic in Type, Not Diagnosed Clinically as Rheumatic Heart Disease (Group IV)

PATIENT SEX AGE			HISTORY	PHYSICAL FINDINGS		LABORATORY FINDINGS			CLINICAL DIAGNOSIS		AUTOPSY FINDINGS		PRINCIPAL ANATOMIC DIAGNOSIS			
		yr		PERI CARDITIS	MURMURS	CONGESTIVE FAILURE	HIGHEST TEMPERATURE °F	SEDIMENTATION RATE	WHITE-CELL COUNT $\times 10^3$	P.R. INTERVAL		PERI-CARDITIS	MYOCARDIAL ASCHOFF BODIES	VALVULITIS		
A	E	F	61	Left hemiparesis coma	0	Mitral systolic	+	105	++	12-14	Normal	Hypertension hypertensive heart disease cerebral thrombosis	None	Cellular with acute necrosis	None	Cerebral encephalomalacia
H	W	M	52	Congestive failure	0	0	+	98.6	—	6-8	Prolonged	Hypertension, hypertensive heart disease	Serous effusion	Cellular	None	Cardiac decompensation
C	B	F	49	Malaise, jaundice	0	0	0	101	—	9-14	—	Carcinoma, head of pancreas broncho-pneumonia	None	Acellular	None	Cardiac decompensation with pulmonary congestion and edema, acute yellow atrophy, early, slight.
S	H	M	62	Cough, weight loss, sore throat	0	Aortic systolic	0	101	—	18	—	Primary tuberculosis arterio-sclerosis	Serous effusion	Atypical	None	Pulmonary tuberculosis

2 cases to hypertension, the third being considered arteriosclerosis. It is significant that the sedimentation rates were not determined in any of these patients and that electrocardiograms were taken in only 1 case. The clinical diagnoses in the cases with congestive failure were hypertension and cerebral hemorrhage in 1 case and hypertension with subarachnoid hemorrhage in another, whereas in a third no etiologic cause of failure was given.

At post-mortem examination the hearts were as characteristic of rheumatic heart disease as those in the preceding two groups. In the myocardium there were numerous Aschoff bodies, which, together with the typical healed valvular deformities, made the diagnosis of rheumatic carditis certain. In several cases the Aschoff bodies appeared to be

tion attributed to hypertension, and the other of cerebral encephalomalacia.

# DISCUSSION

Of the 41 patients presented, the first group, composed of 20 patients, represented the pathologic process in its familiar clinical form. All the patients except 4 were in the first two decades of life, and they demonstrated at various times during the illness one or more of the typical manifestations. This group serves as a contrast to the other three groups, in which the presence of rheumatic activity was not recognized during life.

The second group of patients, 10 in number, differed from the first group in many respects (Table 5). To begin with, although they were all

TABLE 5 Summary of Clinical and Laboratory Data in Two Groups of Cases

GROUP	NO. OF CASES	AVERAGE AGE	CASES WITH PRECEDING INFECTION	CASES WITH JOINT SIGNS OR SYMPTOM	CASES WITH PERICARDITIS	CASES WITH CONGESTIVE FAILURE	TYPE OF TEMPERATURE	CASES WITH ABNORMAL SEDIMENTATION RATE	WHITE CELL COUNTS	CASES WITH PROLONGED PR INTERVAL
I	20	18*	14	15	13	18	High	9†	High	9‡
II	10	41§	3	3	1 (1)	10	Low	2¶	Lower	2

\*Range of 2 to 53 yr.

†Rate slightly abnormal; determination made in 11 cases.

‡Interval determined in 12 cases.

§Range from 12 to 63 yr.

¶Moderately abnormal; determined in 4 cases.

||Interval determined in 8 cases.

somewhat acellular, indicating that the process had passed through the peak of its acuteness, but sufficient necrosis persisted to warrant their inclusion with the cases of acute myocarditis. In 2 patients only an acute valvulitis was present, with no evidence of earlier damage. Two cases presented recurrent acute endocarditis superimposed on old valvular damage.

From the anatomic point of view it appears highly likely that 3 of these patients died of cardiac decompensation, the other 4 dying of massive pulmonary embolism, mesenteric thrombosis, pulmonary tuberculosis and adhesive pericarditis respectively.

## Group IV

In Group IV the average age, which was fifty-six years, was the same as that in the cases in Group III, with a range of forty-nine to sixty-two years (Table 4).

One patient had had a questionable diastolic murmur, and 2 had had congestive failure. As in Group III the histories disclosed nothing to point to rheumatic disease, and the clinical diagnoses again were such as to show no relation to rheumatic heart disease. The acute myocarditis was associated with acute yellow atrophy of the liver in 1 case and with bilateral advanced tuberculosis in another. Of the remaining 2 patients, 1 died of cardiac decompensa-

tion. Known to have had rheumatic heart disease and all were in congestive failure, the disease was considered to be inactive at the time of death. The decompensation was thought to be purely on the basis of previous valvular damage, no element of reactivation of the disease being suspected.

The question obviously arises why this reactivation of the rheumatic carditis was not recognized clinically. The patients as a group gave almost no history suggestive of activation of the disease. Unlike the earlier recognized attacks, the last one was not ushered in with any striking suggestive features such as polyarthritides and sore throat. Perhaps the factor most largely responsible for the failure to recognize active rheumatic heart disease in this group was the age of the patients. As mentioned above, they were at least twenty years older than those in Group I. In 7 cases it is apparent from the clinical records that active infection was not considered to be sufficiently likely to merit close observation of the sedimentation rate and the PR interval. Hence one or both of these important characteristics of active infection are missing from many of the records. Two cases with adequate observations on temperature, sedimentation rate and PR interval may properly be classified as sub-clinical infections. Although occasionally these 2 cases showed transient temperature elevation or

temporary rises in the sedimentation rate, at no time was there any conclusive evidence of activity from the standpoint of history, physical examination or laboratory study. The cases in this group contrast rather strikingly with those presenting initial rheumatic attacks occurring in persons over sixty years of age reported by Ferris and Myers<sup>10</sup> and others,<sup>11, 12</sup> who found even in these older age groups most of the usual manifestations of active rheumatic disease, such as joint pains and polyarthritides. In many cases, however, the clinical diagnosis was not made because of advanced age. In our cases, which were similar to those reported by Hawking<sup>13</sup> and others,<sup>14</sup> activity was present in the absence of the usual clinical signs or with only isolated manifestations.

It is perhaps worth emphasizing at this point that in patients of this age group the diagnosis of active rheumatic heart disease not infrequently depends on minor and often single rheumatic manifestations.

Further evidence of the latency of acute rheumatic myocarditis is brought out by the cases in Group III, in which the presence of rheumatic heart disease was not suspected. As can be seen from Table 3, all these cases presented definite evidence of rheumatic heart disease at autopsy, 5 with old healed valvulitis acquired at an earlier attack, and 2 apparently occurring as an initial attack. The recognition of active rheumatic carditis in these cases was rendered many times more difficult by several factors: the absence of a previous history or present evidence of rheumatic fever, the advanced age, 5 of the 7 patients being approximately sixty years old, and the complicating presence of arteriosclerosis or hypertension, which appeared to offer an adequate explanation for the cardiac failure. Strangely enough, 1 patient presented several of the cardinal manifestations of rheumatic activity — namely, joint pains, signs of pericardial effusion and leukocytosis. Notwithstanding these positive features, the diagnosis of active rheumatic fever was not made, perhaps chiefly because of the patient's age (forty-seven years). It must be pointed out that in 3 of the 7 cases the death was directly attributable to the rheumatic heart disease and consequent cardiac decompensation.

Group IV is perhaps the most difficult to interpret. These patients between forty-nine and sixty-two years of age had no history suggestive of rheumatic heart disease, and the physical examination and laboratory studies shed no further light on the possibility of the presence of this disease. Yet on post-mortem examination in each case acute myocarditis with Aschoff bodies was found without anatomic evidence of pericardial or endocardial involvement. In 2 cases these Aschoff bodies were of the active cellular type, indistinguishable from those found in known rheumatic carditis. In the other 2 cases the cellularity was less striking but

sufficient to warrant inclusion as active rheumatic myocarditis.

Whether, in the absence of other stigmas of rheumatic fever, one may term this involvement rheumatic myocarditis is open to the controversy regarding the specificity of the Aschoff lesion.<sup>8</sup> The myocardial Aschoff lesions in these cases differed in no important respect from those seen in frank rheumatic fever, and it is well known that rheumatic myocarditis may occur as an isolated lesion without valvular or pericardial involvement.<sup>14, 15</sup> One can only say of these cases that they represented insidious latent acute myocarditis, probably rheumatic in origin and associated in 2 cases with anatomic evidence of decompensation.

#### SUMMARY AND CONCLUSIONS

In a review of 41 pathologically proved cases of active rheumatic myocarditis the usual clinical manifestations of activity were sufficiently striking in 20 cases to result in a clinically correct diagnosis. Most of these patients were in the first two decades of life. The remaining 21 cases were not diagnosed as active rheumatic disease during the terminal illness, perhaps the most characteristic feature of this group was the age, which averaged fifty-three years and nine months and, except in 5 cases, was over forty years.

In 10 of these 21 patients a previous diagnosis of rheumatic heart disease had been made, and the terminal cardiac decompensation was considered to have been on a mechanical valvular basis without the complicating presence of myocarditis. Possibly owing to lack of awareness of the significance of myocarditis in these older age groups, adequate observations of the PR interval and sedimentation rate were not made in 7 cases. Although in 2 of the 10 cases at no time was there good clinical evidence of rheumatic activity, in several other cases there were single or minor manifestations of active rheumatic disease.

In 7 more of the clinically undiagnosed cases no diagnosis of rheumatic disease had been made in the past, nor was it entertained during the terminal illness. In all but 1 case rheumatic manifestations were singularly absent from this group, and the disease took what may be termed a truly silent form. It is to be noted, however, that in 3 of these patients, although the clinical disease was silent, from the pathological standpoint death was undoubtedly attributable to decompensated acute rheumatic heart disease.

The 4 remaining patients represented subclinical acute rheumatic myocarditis occurring without associated pericardial or endocardial involvement. In these cases it is likely that the myocardial disease was incidental to the actual cause of death and that therefore the diagnosis could hardly have been suspected clinically.

Active rheumatic heart disease with cardiac involvement in older age groups is frequently clinically unsuspected

The difficulty of clinical recognition of rheumatic activity in older patients can be attributed to several factors in these age groups active carditis assumes in a high percentage of cases an atypical form in which the diagnosis of activity may depend on careful evaluation of isolated rheumatic manifestations, active rheumatic myocarditis as a cause of cardiac failure may be obscured by the presence of complicating diseases, such as hypertension, arteriosclerosis and healed rheumatic valvular disease to which the cardiac decompensation may be reasonably attributed, and, in a certain number of cases, the disease may be entirely silent, rendering clinical recognition difficult if not impossible

The results indicate that, contrary to the general impression, cardiac decompensation in rheumatic heart disease, even in older persons is frequently the result of activity of the disease

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## THE USE AND ABUSE OF CHEMOTHERAPEUTIC AND ANTIBIOTIC AGENTS\*

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TEN years have passed since the sulfonamides were introduced into general therapy in this country. Notable reductions in the case mortality

drugs. The course of gonococcal, staphylococcal and other stubborn bacterial infections has been radically altered by therapy with the sulfonamides

TABLE 1 Present Day Usage of Sulfonamides and Antibiotics in Beta Hemolytic Streptococcus Infections\*

INFECTION	AGENT
Tonsillitis	Sulfadiazine and derivatives; penicillin G‡
Peritonsillar abscess	Sulfadiazine and derivatives; penicillin G‡
Ludwig's angina	Combination of sulfadiazine and derivatives with penicillin G
Acute sinusitis	Sulfadiazine and derivatives; penicillin G‡
Otitis media	Sulfadiazine and derivatives; penicillin G‡
Mastoiditis	Combination of sulfadiazine and derivatives with penicillin G
Meningitis	Combination of sulfadiazine and derivatives with penicillin G
Erysipelas	Sulfadiazine and derivatives; penicillin G‡
Scarlet fever	Sulfadiazine and derivatives; penicillin G‡
Adenitis	Sulfadiazine and derivatives; penicillin G‡
Cellulitis	Sulfadiazine and derivatives; penicillin G‡
Pneumonia	Combination of sulfadiazine and derivatives with penicillin G
Empyema	Combination of sulfadiazine and derivatives with penicillin G
Pericarditis	Combination of sulfadiazine and derivatives with penicillin G
Pericardial seps	Combination of sulfadiazine and derivatives with penicillin G
Septicemia	Combination of sulfadiazine and derivatives with penicillin G
Osteomyelitis	Sulfadiazine and derivatives; penicillin G‡
Ulcers	Sulfadiazine and derivatives; penicillin G‡
Impetigo	Sulfadiazine and derivatives

\*Indications are for oral and parenteral use only. It will be noted that streptomycin and sulfasuximide and similar sulfonamide derivatives should not be used in the infections listed. Penicillin G is contraindicated in impetigo.

†First choice.

‡Second choice

rates of streptococcal, meningococcal and pneumococcal infections have followed the use of these

One can say without exaggeration that the success, as well as the failures, of the sulfonamides stimulated research that led to the development of penicillin and the discovery of streptomycin. Today the physician has a choice of chemotherapeutic and antibiotic agents with which to combat infectious diseases. With several to choose

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from, it is essential that he select the drug wisely, to serve the best interests of the patient

Selection

The physician, when confronted with an infectious process that may respond to one of several chemo-

represent his synthesis of these considerations Too often the newest compound in this group is used, or one that is supposed to be less toxic than others, without due consideration of the cost or the relative toxicity of the various compounds that might be employed It must be remembered that *all the*

TABLE 2 *Present-Day Usage of Sulfonamides and Antibiotics in Infections due to Nonhemolytic or Alpha Streptococci and Other Organisms\**

DISEASE	AGENT
Subacute bacterial endocarditis	Penicillin G
Pneumococcal infections	Sulfadiazine and derivatives†, penicillin G‡
Pneumonia	Sulfadiazine and derivatives†, penicillin G‡
Meningitis	Sulfadiazine and derivatives combined with penicillin G
Peritonitis	Sulfadiazine and derivatives combined with penicillin G
Otitis media	Sulfadiazine and derivatives combined with penicillin G
Mastoiditis	Sulfadiazine and derivatives combined with penicillin G
Sinusitis	Sulfadiazine and derivatives combined with penicillin G
Meningococcal infections	Sulfadiazine and derivatives combined with penicillin G
Gonococcal infections	Sulfadiazine and derivatives†, penicillin G‡
Staphylococcal infections	Sulfadiazine and derivatives†, penicillin G‡
<i>Escherichia coli</i> tissue infections	Sulfadiazine and derivatives†, streptomycin‡
Gas gangrene	Sulfadiazine and derivatives combined with penicillin G
Cholera	Sulfadiazine and derivatives
Tularemia	Streptomycin
Tuberculosis (selected cases)	Streptomycin
Influenzal meningitis	Sulfadiazine and derivatives combined with streptomycin
Plague	Sulfadiazine and derivatives
Infections due to Friedländer bacillus	Sulfadiazine and derivatives combined with streptomycin

\*Indications are for oral and parenteral use only It will be noted that sulfaguanidine and similar sulfonamide derivatives should not be used in the infections listed The drugs are contraindicated in the infections in which their use is not recommended

†First choice.

‡Second choice.

therapeutic or antibiotic agents, should consider the following questions in selecting the drug with which to treat the disease

Which agent will be the most effective?

What is the relative toxicity of the drug in the dosage prescribed?

*sulfonamides and antibiotics in common use are capable of producing serious toxic reactions*

Tables 1, 2 and 3 present in general terms the compounds of choice for the treatment of infections of average severity These choices are based on the considerations discussed above It is to be noted

TABLE 3 *Present-Day Usage of Sulfonamides and Antibiotics in Various Diseases\**

DISEASE	AGENT
Bacillary dysentery	Sulfadiazine and derivatives† sulfaguanidine and other sulfonamides‡
Brucellosis	Sulfadiazine and derivatives (†)†, streptomycin (†)†, sulfadiazine and derivatives combined with streptomycin
Typhoid fever	—
Salmonella infections	—
Chancroid	—
Urinary-tract infections	Sulfadiazine and derivatives
<i>Aerobacter aerogenes</i>	Sulfadiazine and derivatives† streptomycin‡
<i>Esch. coli</i>	Sulfadiazine and derivatives† streptomycin‡
<i>Pseudomonas aeruginosa</i>	Sulfadiazine and derivatives† streptomycin‡
<i>Proteus vulgaris</i>	Sulfadiazine and derivatives† streptomycin‡
Actinomycosis	Sulfadiazine and derivatives†, penicillin G‡
Anthrax	Sulfadiazine and derivatives† streptomycin‡
Trachoma	Sulfadiazine and derivatives
Lymphopathia venereum	Sulfadiazine and derivatives
Ulcerative colitis	Sulfaguanidine and other sulfonamides(†)
Psittacosis	Penicillin G (†)
Dermatitis herpetiformis	Sulfapyridine
Influenza	—
Common cold	—
Rheumatic fever (prophylaxis only)	Sulfadiazine and derivatives
Surgical bowel conditions (preoperative)	Penicillin G
Syphilis	Penicillin G
Yaws	Penicillin G

\*Indications are for oral and parenteral use only The drugs are contraindicated in the infections in which their use is not recommended

†First choice.

‡Second choice.

With what ease can the compound be given?

What will the cost of the agent, or the auxiliary costs of its administration, be to the patient?

All four questions, especially the last two, are important in this day when the costs of medical care are soaring The physician's final decision should

that sulfanilamide and sulfathiazole are not included Either of these drugs may be used when indicated if members of the diazine group of sulfonamides are not available "Sulfaguanidine and other sulfonamides" may be considered to include sulfasuxidine and sulfaphthalidine In all severe cases of

infectious diseases that respond to more than one of these agents, a combination of the two most effective agents should be used

### Dosage

It would be repetitious to outline dosage forms for the various compounds listed above. Directions

of vertigo and deafness rarely occur before the fourth day of streptomycin therapy. Patients should be carefully examined each day for symptoms and signs of eighth-nerve involvement, and the drug should be discontinued immediately if such effects are noted. Skin rashes and urticarial reactions similar to those seen in the course of penicillin

TABLE 4 Incidence of Important Toxic Reactions in the Course of Sulfonamide Therapy in Adult Patients \*

REACTION	SULFANILAMIDE		SULFAPYRIDINE		SULFATHIAZOLE		SULFADIAZINE	
	NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE	NO.	PER CENTAGE
Fever	2910	5.0	3421	3.1	1316	6.0	4194	1.6
Rash	1066	2.0	3171	2.0	1651	5.2	5137	1.3
Acute hemolytic anemia	1630	2.0	2363	1.1	Very rare		Very rare	
Leukopenia	1000	2.0	2026	2.1	1231	1.6	4601	1.5
Agranulocytosis	1000	0.1	1444	0.8	Rare		Rare	
Hematuria, gross and microscopic	Extremely rare		3899	4.6	1749	4.7	5137	1.7
Oliguria, anuria or azotemia	Extremely rare		2360	2.9	1124	1.1	5137	0.4
Hepatitis	1000	0.6	Rare		Very rare		Very rare	
Averages		11.9		15.9		18.6		6.5

\* These figures are based on the reported incidence of toxic reactions, personal experience and in the instance of sulfadiazine, on data furnished by Finland et al.<sup>1</sup>

regarding dosage are contained in *New and Non-official Remedies*,<sup>1</sup> to which the physician is referred for such information. Also, it can be said that accurate directions for using these drugs are contained in the package inserts of the brands that have been accepted by the Council on Pharmacy and Chemistry of the American Medical Association.

### Toxicity

Table 4 outlines the incidence of important toxic reactions noted in the course of sulfonamide therapy. It is obvious from the data presented that sulfadiazine is the least toxic of the four drugs listed. Although comparable figures are not readily available, sulfamerazine and sulfapyrazine appear to be somewhat less toxic than sulfadiazine.

Toxic reactions have also been observed after the administration of the antibiotics (Table 5). Initially, it was thought that penicillin was relatively non-toxic. As experience with this antibiotic has increased, however, toxic reactions, especially those of the urticarial and dermal type, have become more frequent. I have witnessed urticarial reactions, which were not only most distressing and painful to the patients but also costly, because the patients were incapacitated for weeks. All varieties from mild erythematous rashes to dermatitis exfoliativa have been noted. Penicillin is not without its danger.

When streptomycin was initially introduced as a therapeutic agent, reactions similar to those following the administration of histamine were frequent. This type of reaction has practically disappeared as the antibiotic substance has become increasingly purified. A most serious and distressing reaction characterized by vertigo and impairment of hearing, however, has been observed in the course of streptomycin therapy. In certain cases the vertigo and deafness appear to be permanent. The symp-

therapy have also been noted after streptomycin administration.

It is my opinion that the time has come to inveigh against the local use of sulfonamides and the antibiotics. There is little evidence that when these agents are used externally as dusting powders, or in creams, lotions or salves, the beneficial effects

TABLE 5 Toxic Reactions with the Antibiotics

REACTION	PENICILLIN	STREPTOMYCIN
Dermatitis	Common	Common
Urticaria	Common	Common
Fever	Common	Common
Headache	—	Occasional
Histamine-like	—	Rare
Red cells and casts	—	Common if urine is acid
Neuritis	Rare	Not described
Eosinophilia	—	Very common
Vertigo	—	Common
Deafness	—	Occasional
Agranulocytosis	—	Rare

weigh the known risk of sensitizing the patient. Nothing appears to be gained from treating a minor infection locally (when parenteral or oral therapy will achieve the same end) if the patient becomes sensitized to the drug and is thus deprived of its valuable effects, when later he may have an infection in which the agent might be life saving.

### CONCLUSION

With a variety of chemotherapeutic and antibiotic agents at the physician's disposal for the treatment of infectious diseases, careful consideration must be given to the selection of the agent that best suits the needs of the patient.

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## THE OPERATIVE AND POSTOPERATIVE MANAGEMENT OF HYPERTENSIVE PATIENTS UNDERGOING THORACOLUMBAR SYMPATHECTOMY

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**T**HE surgical treatment of hypertension had its origin in the pioneer work of Crile,<sup>1</sup> Adson et al.,<sup>2,3</sup> Page and Heuer,<sup>4</sup> Peet<sup>5</sup> and others, but it was not until the brilliant clinical studies of Smithwick,<sup>6</sup> first published in 1940, that a truly effective operative procedure was available. The extent of the operation described by Smithwick and employed by him for the past eight years included removal of the thoracolumbar chain from the eighth or ninth thoracic ganglion through the first or second lumbar ganglion, along with portions of the greater, lesser and least splanchnic nerves.

Hinton and Lord<sup>7</sup> reported 152 hypertensive patients operated on by the Smithwick technic between February, 1942, and May, 1945. Follow-up study after six months showed that 53 per cent had a fall in the level of the diastolic blood pressure of 20 points or more—that is, a Group I or Group II result according to Smithwick's classification. Only 30 per cent had diastolic readings below 100. In general the majority of patients selected had suffered from advanced hypertension, essential and malignant, and only a few cases could be classified as falling into the relatively mild or early form, the Group II of Keith, Wagener and Barker.<sup>8</sup>

In the hope of increasing the percentage of patients obtaining significant falls in the postoperative diastolic blood pressure we gradually extended the operation until by December, 1945, the majority underwent an extensive thoracolumbar sympathectomy, which included removal of the sympathetic chain from the third or fourth thoracic through the second or third lumbar segment, along with the entire greater, lesser and least splanchnic nerves. With sufficiently long instruments this procedure can usually be accomplished through an exposure obtained by removal of the tenth rib in toto. This operative approach has recently been described in detail.<sup>9</sup> A six months' follow-up study of 15 cases in which the extensive sympathectomy had been carried out revealed that 93 per cent of patients had Group I or II diastolic falls and 80 per cent had diastolic blood pressure levels under 100. The hospital mortality in 120 patients undergoing the extensive operation was approximately 6 per cent, all deaths occurring in patients with advanced hypertension.

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As a result of our experience with 400 patients subjected to the two-stage thoracolumbar sympathectomy during the past five years, certain principles of management during the operative and postoperative periods have evolved. The patients on whom the extensive sympathectomy is carried out need every possible adjunct to bring them through without serious complications due either to their disease—that is, coronary occlusion, heart failure, cerebral accident or renal failure—or to a complication of the thoracotomy, such as pleural effusion, pneumothorax, atelectasis or pneumonia.

There are two basic problems to be handled during the operative and early post-operative periods: the maintenance of an adequate blood pressure and thereby avoidance of a marked systolic fall to levels of 90 or lower,—falls that can occur with alarming suddenness especially during and after the second-stage procedure,—and, secondly, the management of the thoracotomy during and after operation.

The maintenance of a relatively stable pressure has been best achieved during the operation by the use of 2 cc of a 1 per cent solution of Neo-Syneprine in 1000 cc of 5 per cent glucose in distilled water administered intravenously and, postoperatively, by the same fluid with 1 cc of Neo-Syneprine per 1000 cc of solution until the systolic blood pressure has been stabilized at 90 or 100 or higher. This may take only a few hours or as long as forty-eight hours. Before the adoption of this method, which was suggested by Dr Milton C Peterson, head of the Department of Anesthesiology of the New York Post-Graduate Hospital, the anesthetist injected intramuscularly or intravenously 2 or 3 minims of Neo-Syneprine when necessary, and the same procedure was used postoperatively. Figures 1 and 2 show the blood-pressure recordings by the anesthetist during the second-stage procedure in 2 cases in which the intermittent method was used in 1 and the continuous technic in the other. In the latter procedure, if the blood pressure falls, the infusion is speeded, and when stabilization has been achieved, it is slowed.

We have found that moderate anemia develops after each stage of the extensive sympathectomy, probably owing to oozing into the extrapleural and intrapleural spaces during the early postoperative period, and for that reason a 500-cc blood transfusion is routinely administered immediately after each stage.

The second major problem in these patients is to obtain hemostasis and to deal with the open thorax

during the operation and to prevent serious hemothorax, pneumothorax, atelectasis and pneumonia postoperatively. Grimson<sup>10</sup> has recently stated his position as follows: a closed anesthetic system is employed, an intratracheal tube being used only occasionally, the pleural cavity is deliberately entered through a partial third-rib and a longer tenth-rib resection, and the chain removed from the stellate ganglion through the first or second lumbar segment, inclusively, followed by the use of a closed-tube suction drainage of the pleural cavity for two or three days. We have also made use of a closed anesthetic system, usually with an intratracheal tube. Recently, we have begun a series without such a tube, and the management in the

Hemostasis is not a simple matter in this procedure, and one of the frequent complications has

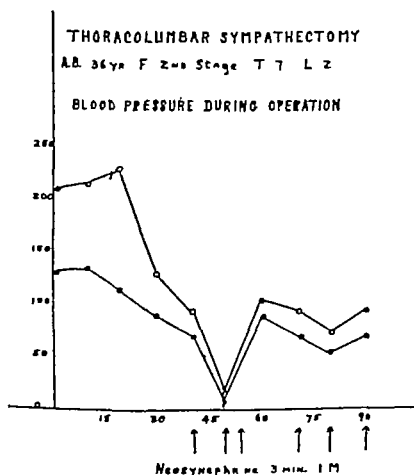


FIGURE 1

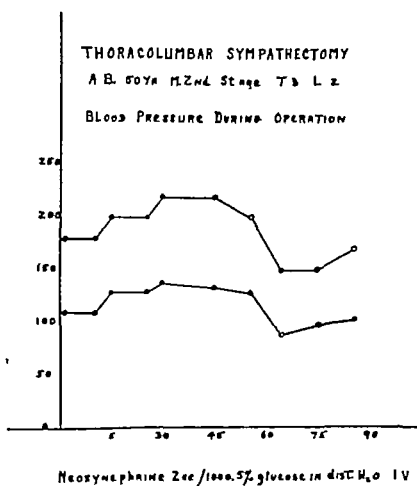


FIGURE 2

been the development of fluid in the chest post-operatively. Grimson<sup>10</sup> has had similar difficulty

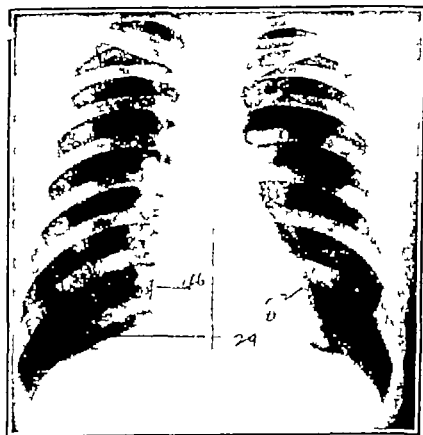


FIGURE 3

hands of experienced anesthetists has been for the most part satisfactory. One point should be emphasized: this extensive sympathectomy should be carried out only when an anesthetist thoroughly familiar with open-chest operative procedures is administering the anesthetic. Although in our technique the parietal pleura is stripped from the chest wall from the diaphragm to the apex of the thorax, it is usually torn to a greater or lesser extent so that air readily passes into the intrapleural space.

Anesthetic agents have included ether, cyclopropane and ethylene, and the indications for and contraindications against these agents may best be found in reports by Phelps and Burdick<sup>11</sup> and Burdick, Phelps and Peterson.<sup>12</sup>

by his method of approach. In addition to the clam <sup>ligature</sup>, there are at one's disposal



temporary pressure on the venous bleeder against the vertebral column, which is often satisfactory, silver clips, oxycel and other hemostatic absorbable agents, bone wax and finally the electrocautery. We have not used the last because of the fear of an explosion in the presence of such potentially dangerous anesthetic agents and the open pleura. Furthermore, the most serious difficulty with hemorrhage is presented by an accidental tear of an intercostal artery high in the chest cavity, such as the third, fourth or fifth.

When hemostasis has been obtained after the removal of the sympathetic chain and suture of the

Other factors of importance in the postoperative management are as follows

Oxygen therapy (by nasal catheter, mask or tent) is used in patients with low preoperative cardiac reserve.

Digitalization of patients preoperatively is effected when evidence of actual or impending congestive heart failure is present, and the drug is continued after operation.

Penicillin in liberal doses is given intramuscularly when the operation has been more difficult than usual or when the pleura has been widely

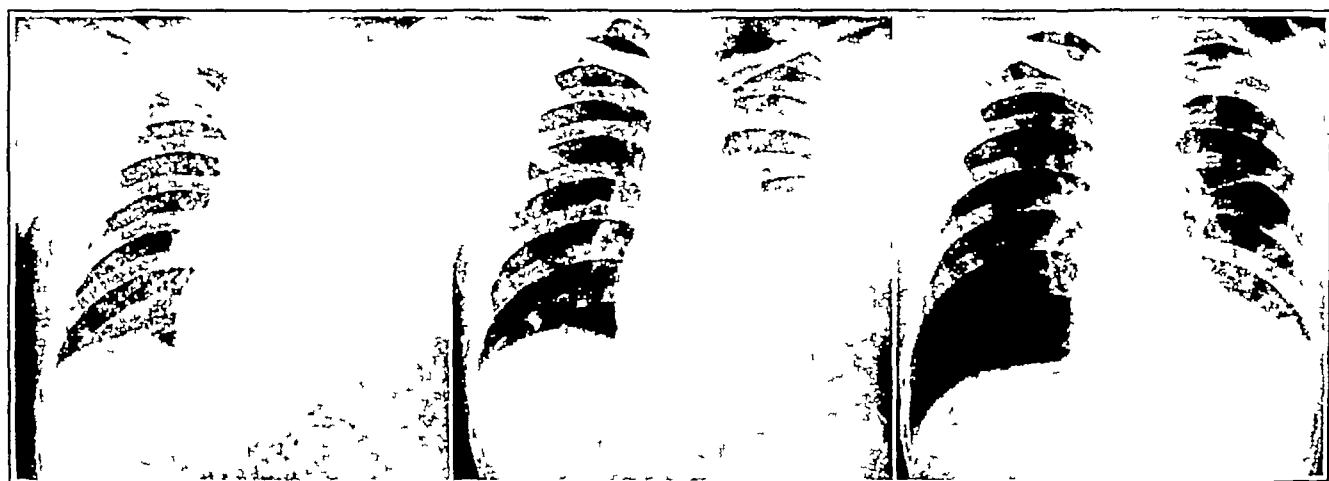


FIGURE 4

diaphragm, the chest wall is closed around a large rubber catheter placed in the pleural space. Air is completely aspirated, the catheter removed, and the skin closed without drainage. During the entire postoperative period, but particularly during the first forty-eight hours, careful, repeated bedside examination of the chest must be made. Signs of fluid or atelectasis (usually due to fluid), or both, are promptly checked by an x-ray film of the chest taken with a portable apparatus, and aspiration with a large (No. 15) needle is carried out. Figure 3 shows the preoperative radiogram of a patient who postoperatively developed signs of fluid on the left side. Figure 4 illustrates radiograms taken on the sixth, tenth and thirteenth postoperative days. Aspiration of 525, 1050 and 900 cc. were made on the seventh, ninth and twelfth days. It is interesting that significant fluid accumulated only after the first operation, and after a second-stage sympathectomy on the right side no fluid developed. In patients with poor cardiac reserve unrecognized pleural effusions (usually hemorrhagic) may be of the gravest significance, and prompt recognition and treatment may be life saving.

torn, with potential trauma to the lung by retraction.

Study of the blood urea nitrogen and the nonprotein nitrogen on the first postoperative day is made to determine to what degree renal function has been disturbed. Occasionally, the blood chemical constituents become greatly elevated after operation, in spite of fairly adequate preoperative renal function, and only by energetic treatment with large amounts of 10 per cent glucose in distilled water and blood transfusions can a serious degree of uremia be avoided. No patient is given physiologic saline solution intravenously during or after either stage of the procedure.

The red-cell count is checked on the first postoperative day, and if an anemia is present in spite of the regular transfusion, further transfusions are administered.

Early ambulation is practiced only after the first-stage sympathectomy. After the second operation patients are allowed up when the blood pressure has been stabilized and when the cerebral and cardiac functions are adequate.

Finally, in a few patients, who preoperatively had had either a stroke or a coronary occlusion, we have cautiously used subcutaneous heparin in Pitkin menstruum postoperatively. Coronary thrombosis is theoretically more likely in a patient who previously has had such an accident and in whom the blood pressure has been reduced sharply from hypertensive to normotensive levels. That this accident does not occur more frequently is remarkable, but the careful use of heparin may be valuable in selected cases. So far, no serious untoward effect has followed the administration of this anticoagulant.

### SUMMARY

In the operative and postoperative management of hypertensive patients undergoing extensive thoracolumbar sympathectomy, including the third or fourth thoracic through the second or third lumbar ganglia, certain factors are of value: the use of 2 cc of a 1 per cent solution of Neo-Synephrine in the intravenous fluid given during and after each operative stage, and closure of the chest incision without drainage, followed by careful postoperative check-up by physical examination and portable x-ray films.

The types of anesthetic agent, the use of oxygen, digitalis, penicillin, studies of the blood chemistry and red-cell count, early ambulation and heparinization are discussed.

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## PNEUMOPERITONEUM FOLLOWING GASTROSCOPY APPARENTLY WITHOUT PERFORATION

### Report of a Case

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**P**NEMUMPERITONEUM following the usually benign procedure of gastroscopy is so startling when it occurs that an additional report is believed to be of value. There have been only three previous reports of this condition. In the first, presented by Schiff<sup>1</sup> in 1941, the only finding was subdiaphragmatic air at x-ray examination four days after the gastroscopy. In the case reported by Schindler<sup>2</sup> in 1945, laparotomy was performed three hours after the onset of the pneumoperitoneum, methylene blue was injected into the gastric lumen, and oxygen blown into the stomach under a pressure of 60 pounds, but no perforation was found. Berk<sup>3</sup> reported the third case, in which, again, no perforation could be found at laparotomy. Schindler postulated a slit-like perforation of the stomach that promptly healed, although no trace of it was present.

The following case† differs from those previously reported in that a large gastric ulcer was present (Fig. 1).

E. L., a 42-year-old truck driver, was admitted to the hospital on March 5, 1947, for gastroscopy, which was unsatisfactory. The instrument passed with ease but the stomach was difficult to inflate and contained considerable mucus. An ulceration was momentarily visualized, but not sufficiently to make a diagnosis. Because of the large amount of mucus the instrument was removed. The patient belched copiously but did not complain of pain. An Ewald tube was passed and an attempt was made to aspirate the mucus. Nothing was obtained. The gastroscope was reintroduced easily. The stomach did not inflate to any degree and the examination was terminated. The abdomen was distended but the patient could not belch any air. The distention continued all day.

Physical examination showed the abdomen to be tight and tympanic; the liver dullness had disappeared. Both leaves of the diaphragm were high. Examination of the scrotum revealed emphysema. The patient was not in shock and had no pain, but he became dizzy if his position was changed. The temperature, pulse and respirations were normal.

†Reported through the courtesy of Dr. Leo Lyock of Malden, Massachusetts.

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Examination of the blood disclosed a white-cell count of 20,000. A plain film of the abdomen demonstrated a marked pneumoperitoneum (Fig 2).

The diagnosis was pneumoperitoneum without apparent perforation.

Since the only complaint throughout the day was a feeling of fullness, the patient was allowed to continue his ulcer management, which he did without distress or nausea. However, during the early evening, the temperature, which had been normal all day, began to rise, and it was deemed in-

On March 8 the course was uneventful. The emphysema was still present in the carotid sheath and suprapubically.

Pathological examination by Dr M V MacKenzie revealed a roughly triangular piece of stomach wall measuring 5.0 by 3.0 by 1.5 cm. The mucosa was velvety, edematous and grayish white. In the center there was a punched-out ulcer crater measuring 1.2 by 2 cm and extending approximately 0.5 cm below the surface. The edges were rolled, and the base contained adherent, fibrous tags of tissue. The serosal surface was spongy and edematous, with adherent fibrous tags of tissue and many areas of hemorrhage. Section revealed a homogeneous, edematous, pink-gray surface with many flecks of necrotic tissue and areas of hemorrhage. The ulceration had extended through the muscularis but had not, apparently, penetrated the serosa. The presence of dilated lymphatic vessels (including the perineural vessels) suggested a possible pathway for the air.

The gross diagnosis was chronic penetrating gastric ulcer, with necrosis and marked edema of the surrounding tissue.

The patient experienced no abdominal pain, beyond the usual discomfort associated with dis-



FIGURE 1 Roentgenogram Showing Large Gastric Ulcer on the Lesser Curvature

advisable to continue the policy of noninterference. Accordingly, exploration was decided on.

At operation\* under spinal anesthesia a high left rectus muscle incision was made. The peritoneum was under such marked tension that it was difficult to grasp it with forceps. Opening released a gust of air much more violent than that encountered in the ordinary case of perforated ulcer. The abdomen collapsed. There was no intestinal distention, no free fluid and no fibrin. The stomach was thickened, and there were emphysematous blebs along the lesser curvature and extending into the fundus. There was no perforation on the anterior gastric surface. The lesser omental sac was opened through the omentum and the posterior wall inspected, but there was no perforation. Marked retroperitoneal emphysema was observed over the aorta. Since it seemed that there must be a microscopic perforation—probably retroperitoneal—and since the ulcer was not definitely palpable, the stomach was opened. An ulcer crater, almost 2 cm in diameter, was discovered on the posterior wall, extending onto the lesser curvature at its mid-portion. The lesser omentum was dissected from the lesser curvature, and the right and left gastric arteries were ligated. A wedge resection was done after the method of Walton. The mucous membrane was approximated with silk. Gastroenterostomy was not performed. Rents in the greater and lesser omentum were repaired. The abdomen was closed in layers without drainage.

\*Performed by Dr W J Reynolds



FIGURE 2 Roentgenogram of Abdomen Showing Marked Pneumoperitoneum

tention, at any time during the gastroscopic examination. The scrotal emphysema was noted late in the day after gastroscopy, but the carotid sheath and suprapubic emphysema did not appear until the following morning. In this case, the Walton resection of the ulcer was justified because of the interstitial emphysema of the wall of the stomach. It is doubtful if the sutures of a subtotal gastrectomy would have held in this tissue.

The possible anatomic route for the spread of the emphysema is suggested in the description of the microscopical appearance of the tissue taken from the ulcer. The perineural lymphatic vessels were dilated more than is seen in a section through an ordinary gastric ulcer. The interstitial emphysema of the stomach wall may be explained on this basis. The free air in the peritoneal cavity had probably been diffused through the very thin base of the ulcer. The peripheral emphysema of the scrotum along the fascial planes, in the neck and in the abdominal wall may have been due to the passage of air along the lymphatic and blood vessels of the stomach wall.

In 2 of the previously reported cases,<sup>2,3</sup> as in the case reported above, laparotomy was performed soon after the occurrence of the pneumoperitoneum. Because of the rarity of the complication, laparotomy was justified, to find and repair any possible perforation. In the future, however, if I encounter a similar case, I shall not be so anxious to have the

patient explored, but shall at once put a needle of large caliber into the abdomen, with the patient lying on his back, and attempt to remove the free air in the peritoneum by this means, waiting for further signs of perforation before asking for a laparotomy.

#### SUMMARY

A case of pneumoperitoneum following gastroscopy is reported.

A brief review of the literature is presented.

A suggestion regarding the management of such cases is made.

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## MEDICAL PROGRESS

### INFLUENZA\*

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INFLUENZA is an old and well established disease that has appeared in epidemics and pandemics since before the seventeenth century. Despite its long history, however, the cause or causes of both epidemic and pandemic influenza remained unknown until fifteen years ago. Since then, remarkable progress in the methods of study and knowledge of epidemic influenza has taken place. Epidemic influenza has been established as a virus infection caused by one or the other of two very similar agents, methods have been devised that have permitted chemical and physical characterization of the viruses, re-evaluation of the clinical and epidemiologic nature of influenza has been made possible on the basis of a simple and specific laboratory diagnostic test, and, finally, a vaccine that holds some promise for the ultimate prevention and control of the disease has been developed. The cause of pandemic influenza is still unknown. The following discussion is an attempt to summarize recent progress, with no intent exhaustively to review the literature.

#### CAUSE OF EPIDEMIC INFLUENZA

In 1933 Smith, Andrewes and Laidlaw,<sup>1</sup> in England, accomplished for the first time the transmission of infection from a human case of influenza to an animal, the ferret. They determined that the agent was a virus that, immunologically, was causally related to the human disease. In the following year, Francis<sup>2</sup> confirmed this observation in the United States and isolated, from a specimen obtained in Puerto Rico, a similar strain, termed "PR8," which has been widely used for investigative purposes in this country. It soon became apparent, however, that strains of this immunologic character were not responsible for all the outbreaks of acute respiratory disease resembling influenza clinically and epidemiologically. In 1940 Francis<sup>3</sup> isolated in ferrets a new strain of influenza virus, termed the "Lee" strain, which was immunologically distinct from the former strains. A similar strain was isolated in the same year by Magill.<sup>4</sup> The two types of virus are now known as influenza virus A, of which the PR8 strain is an example, and influenza virus B, typified by the Lee strain.<sup>5</sup>

Thus, two similar but immunologically distinct viruses cause human influenza. Comparable situa-

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†Professor of preventive medicine and associate professor of medicine, Western Reserve University School of Medicine; associate physician, University Hospitals.

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virus particles. Such data on diameter and water content of the influenza viruses are given in Table 1.

In addition to the methods of study described above, it is now possible to photograph the virus particles themselves by means of the electron microscope and to make direct observations of the size and shape of the images on photographic plates or prints. Direct measurement of the diameter of influenza-virus particles shows moderate variation in size, with an average diameter of approximately 100 millimicrons, which is about one tenth the diameter of the smallest bacteria.

The human influenza viruses A and B and the swine influenza virus are indistinguishable under the electron microscope. Purified preparations appear

molecular in nature but have a behavior and structure indicative of organized cell-like bodies surrounded by a semipermeable limiting membrane.<sup>21</sup>

### Biologic Characteristics

Since the adaptation of the influenza viruses to the mouse and embryonated egg, the biologic properties of the agents have been extensively studied



FIGURE 1 Electron Micrograph of Influenza Virus A by Usual Technique (x 46,000)



FIGURE 2 Electron Micrograph of Influenza Virus A by Shadow Technique Employing Metallic Chromium (x 50,000)

to consist of rounded or bean-shaped, cell-like particles when examined by the usual technique, which gives a two-dimensional image (Fig 1). Recently, Williams and Wyckoff<sup>22</sup> described a "shadow" technique, which introduces a three-dimensional appearance, brought about by the deposition at an angle of a thin layer of vaporized metal over the dried film of virus. The "shadow" is that area, behind the particle, on which no metal is deposited. Viewed by this technique, the influenza-virus particle appears as a more or less spherical body, varying somewhat in size and shape (Fig 2).

Although the full significance of these observations has not yet been determined, there is increasing evidence that the influenza viruses are not

The infectivity for mice and eggs provided a means of quantitating the amount of virus in a given preparation. This activity, in turn, was found to be neutralized by specific antiserums, which permitted comparison of the antigenic composition of different strains of virus and also serologic diagnosis of human infection. Complement fixation was similarly employed. The two techniques of neutralization and complement fixation have now been largely replaced by a simpler and less expensive test *in vitro*. In 1941 Hirst,<sup>23</sup> and independently McClelland and Hare,<sup>24</sup> observed that chicken red cells were agglutinated by allantoic fluid containing influenza virus, and that such agglutination could be inhibited by immune serum. On the basis of this property of the virus, an *in vitro* test that permits the rapid determination of the virus content of an infected fluid or of the amount of antibody in a serum was developed.<sup>25, 26</sup> Further study of the mechanism of the reaction revealed that the virus was adsorbed to the erythrocytes prior to their agglutination and that, under proper condi-

tions, it could be concentrated by elution from the cells<sup>37, 38</sup> The discovery and application of this biologic property constitute a major contribution to the academic and practical study of influenza. The reaction has been utilized for fundamental investigations of the characteristics of strains of virus as they are isolated from human patients and adapted to other tissues. It has been of value for concentration and partial purification in the preparation of vaccines and as a preliminary step before further purification by ultracentrifugation. Finally, it has provided the basis for a simple method of con-



FIGURE 3 *Electron Micrograph of Influenza-Virus Vaccine*  
( $\times 35,000$ )

firming the diagnosis of influenza in the laboratory.

Preparations of concentrated and partially purified influenza viruses have provided laboratory investigators with more highly refined reagents for study of the biologic characteristics of the agent than were previously available. Such materials have been utilized not only for the evaluation of serologic methods for diagnosis but also for the study of the immunizing capacity of the viruses in man and in animals<sup>39-48</sup> The present influenza-virus vaccine is one of the results of this work (Fig 3). A toxic action, apparently inherent in certain strains of living influenza virus, has also been demonstrated in both crude and partially purified preparations<sup>48a</sup> The toxic activity is destroyed when the virus is killed by heat or formalin.

An additional biologic characteristic of influenza viruses that warrants consideration here is the considerable variation in the antigenic composition of individual strains of influenza virus A. For example, the strains isolated from patients during

the late winter and spring of 1946-1947 differed antigenically from the PR8 strain to such an extent that serums drawn during the acute and convalescent phases showed no change in antibody titer when tested with the PR8 strain, and yet showed a definite rise in titer to the newly isolated homologous strain<sup>49, 50</sup> Such changes in the characteristics of influenza virus A, which may be due to true mutation, are of great academic interest to those seeking an understanding of the biologic behavior of influenza<sup>51</sup> They are perhaps of even greater practical importance to those concerned with the laboratory diagnosis of influenza and the preparation of influenza-virus vaccines, as indicated below.

#### CLINICAL CHARACTERISTICS

Influenza is generally considered as a dramatic and acute respiratory disease<sup>52, 53</sup> The onset is often described as sudden and abrupt—so much so that the patient may give the exact hour, prior to which he felt well and after which he was ill. Occasionally fainting or collapse may be the first sign of infection. The early complaints are those of headache, pain in the eyeballs and on movements of the eyes, pain in the back and muscles, malaise, fatigue, weakness or dizziness, chilliness and feverishness. Respiratory symptoms, such as coryza, husky voice, sore throat and dry cough, may or may not be prominent and usually appear after the more marked constitutional symptoms. On physical examination, the patient appears to be acutely ill and markedly prostrated. The temperature is elevated, and there is a relative bradycardia. The face is flushed. Cyanosis may be present, and the skin is occasionally of a peculiar purplish or heliotropic hue. Conjunctivitis is prominent, and the throat appears injected but dry, with a "granular" appearance. The remainder of the physical examination is noncontributory, although occasionally moist rales and rhonchi may be heard in the chest. Leukopenia is the rule.

The course of the illness is characterized by a brisk fever, lasting three to five days and often diphasic. Defervescence is accompanied and followed by marked asthenia. Complications are infrequent, apart from pandemics, and vary in type from pneumonia to sinusitis. The pneumonia is occasionally caused by the virus but is usually due to a secondary or simultaneous bacterial invasion with such organisms as pneumococci, beta-hemolytic streptococci, staphylococci and influenza bacilli. Such an infection may be fulminating and rapidly fatal.

This is essentially the "textbook picture" and is drawn, to a large extent, from observations made during the catastrophic pandemics of influenza. Since 1920, particularly since isolation of the influenza viruses permitted laboratory confirmation of the clinical diagnosis, the clinical picture has

been shown to be much more variable and less striking. During the period of an influenza epidemic, the majority of patients seeking medical care for respiratory illness show laboratory evidence of infection with the influenza virus, almost regardless of the clinical characteristics presented. In non-influenza periods, the reverse is true. If one compares the frequency of symptoms and signs in two such groups of patients, selected on a laboratory basis as "influenza" and "noninfluenza respiratory disease," it will be found that the former group more nearly approaches the textbook picture. In the epidemic of influenza A during the winter of 1943-1944, for example, it was observed that a sudden onset occurred in 35 per cent of cases of influenza in contrast to 19 per cent of the non-influenza cases. The values were 94 and 82 per cent for feverishness, 70 and 53 per cent for malaise, 42 and 69 per cent for sore throat and 84 and 85 per cent for cough, respectively. On physical examination, 32 per cent of patients with influenza were considered to be moderately or severely ill, whereas only 10 per cent of the "noninfluenza" cases were so classified. The signs of flushed face were found in 45 and 22 per cent, of injected conjunctiva in 46 and 21 per cent, of pharyngeal injection in 6 and 13 per cent, and of rales in the lungs in 11 and 6 per cent, respectively.<sup>11-16</sup> It is thus apparent that cases of influenza, as a group, present a clinical syndrome that differs significantly from that of noninfluenza respiratory disease. The same symptoms and signs, however, occur frequently enough in patients of both groups to prevent a definitive clinical diagnosis in a single patient without laboratory confirmation.

In epidemic periods, moreover, inapparent or subclinical infection with the influenza virus, detectable serologically, occurs two or three times more frequently than that of clinically recognizable influenza.<sup>17-19</sup> Influenza must therefore be considered a respiratory disease that varies in its clinical nature from a symptomless infection to a severe and at times rapidly fatal disease.

There is now no doubt that sporadic infection with either influenza virus A or B may occur in nonepidemic periods, as proved both serologically and by isolation of the virus.<sup>20-22</sup> Such cases, however, are almost invariably detected by laboratory methods. The clinical diagnosis of influenza A or B in nonepidemic periods is usually in error.

#### DIAGNOSIS

Since the clinical picture in the individual patient, or in the sporadic case, is not a reliable indication of the occurrence of influenza, the question naturally arises regarding the means by which influenza A or B can be diagnosed. Generally, such a diagnosis can be based most reliably on a combination of clinical and epidemiologic data. The occurrence of an unusual number of cases of respiratory illness,

many of which exhibit the clinical features associated with influenza, is strong presumptive evidence in favor of the diagnosis of influenza. Confirmation of the diagnosis, however, must be made in the laboratory. Two general methods are available: isolation of the virus and determination of the antibody titers of the patients' sera.

Isolation of the virus is the more difficult and expensive of the two methods. Satisfactory specimens for this purpose may be obtained by washing the patient's nose and throat, or having him gargle, with nutrient broth or buffered saline solution. Such specimens should be collected prior to the fourth day of illness, since the virus is rarely found after that time. The virus may then be sought by the intranasal inoculation of ferrets or by the inoculation of embryonated eggs.<sup>23-25</sup> When the latter procedure is employed, bacterial infection may be prevented by filtration of the washings or by the addition of sulfonamides and antibiotic agents.<sup>26-28</sup> The presence of the virus in ferrets is indicated by fever and injection of the nasal turbinates, and after passage to additional ferrets, by the production of pneumonic lesions. In eggs, the virus may be detected by its ability to agglutinate erythrocytes. Once established in either ferrets or eggs, the strain may be identified as influenza virus A or B by immunologic methods employing known antisera for each of the two types of virus.

Diagnosis by determination of the antibody titers of the patients' sera requires the collection of two specimens of serum, one obtained during the acute phase of the disease, preferably before the fifth day, and the other, a convalescent specimen, obtained about the fourteenth day of disease or thereafter. These sera are then titrated for antibody content with a known strain of influenza virus A and one of virus B. Such determinations may be performed by measuring the capacity of the sera to inhibit agglutination of chicken erythrocytes by the virus (agglutinin-inhibition test), by complement fixation or by titrating the capacity of the sera to prevent the infection of mice or eggs by known quantities of virus (neutralization test). The simplest of these determinations and the one most widely used today is the agglutinin-inhibition test. A fourfold or greater increase in antibody titer for one or the other of the two viruses, between sera drawn during the acute and convalescent phases, is generally accepted as indicative of specific infection with that type of influenza virus. It is important that both sera be examined on the same day with the same set of reagents to avoid differences in titer due to technical variations in the tests. It is also essential that this test be carried out with the strain causing the current epidemic, when that strain is available.<sup>29-30</sup>

Neither of these laboratory procedures will permit more than a retrospective or confirmatory diagnosis in an individual patient because of the time required



for their performance. With unusually good fortune, the virus may be isolated in eggs and identified within forty-eight to seventy-two hours from the time of collection of the washing. More frequently from one to three weeks is necessary. Similarly, serologic diagnosis cannot be made for at least nine to fourteen days after the onset of illness, because of the time required for antibody formation in the patient. The development of a rapid diagnostic test would be a major contribution to the problem of influenza.

### TREATMENT

There is no specific agent available for the treatment of influenza. As with other virus diseases, specific antiserum does not alter the course of the disease once the infection is sufficiently established to be recognized as a clinical illness. The sulfonamide drugs and penicillin have no effect on either the virus or the clinical disease. A great deal of time and effort has been and is being spent in the search for chemical or antibiotic agents that might be active against viruses without damaging the host cells — a requirement that must be met before successful therapy will be attained. Although the results with nitroakridin<sup>69</sup> and with various complex polysaccharides<sup>69a, 69b</sup> appear to be hopeful, no agent has yet been found that can be recommended for clinical use.

The treatment of uncomplicated influenza thus consists of supportive measures, such as bed rest, antipyretics and sedation as indicated, and fluids sufficient to give an output of at least 1000 to 1500 cc per day. Steam inhalations frequently relieve to a considerable extent the symptoms of irritation of the respiratory tract. The bacterial complications of influenza should be treated with sulfonamides or antibiotic agents in the same way that similar bacterial infections are treated in the absence of influenza. Penicillin is now the agent of choice when the causative organism is a beta-hemolytic streptococcus, a pneumococcus or a staphylococcus. Streptomycin may be effective when the organism is a gram-negative bacillus, such as *Haemophilus influenzae*.<sup>70</sup>

At present the routine use of sulfonamides or antibiotics for the prevention of complications appears to be neither necessary nor desirable, since their administration is not without the hazards of sensitization and toxic reactions. In the epidemics of influenza that have occurred since 1920, the incidence of complications has been extremely low, and the mortality even lower. Prophylactic use of these agents may be of value, however, in patients who are most severely ill and in those who are harboring pathogenic bacteria in the upper respiratory passages. In the 1940-1941 epidemic of influenza A, for example, *Staphylococcus aureus* was found with unusual frequency in throat cultures of patients with influenza, and pneumonia due to this

organism was an outstanding feature of the epidemic.<sup>19, 20</sup> It seems reasonable to expect that these antibacterial drugs will be of prophylactic as well as therapeutic value in the event of another pandemic of influenza.

### PERIODIC RECURRENCE OF EPIDEMIC INFLUENZA

For a number of years, the periodic recurrence of influenza has been of considerable interest to biostatisticians, epidemiologists and others concerned with the cyclic occurrence of infectious disease and the reasons for such behavior. These studies, generally considered to be of academic interest only, assumed practical importance during the war. Predictions of the occurrence of epidemics were sought not only to prepare for the hospitalization and care of the casualties from influenza but also to indicate the most effective time for administration of the relatively limited supply of influenza-virus vaccine. If it were possible reliably to predict the recurrence of influenza A or B, indiscriminate use of the vaccine could be avoided.

Such predictions, on a world-wide basis, were not possible then and are not now, because the usual epidemics of influenza do not occur simultaneously throughout the world.<sup>71</sup> In the United States, however, a more consistent pattern of recurrence seems to obtain. In the brief period since the identification of the two influenza viruses, influenza A has occurred at an interval of two to three years and influenza B at an interval of four to six years, as demonstrated serologically and by isolation of the viruses.<sup>7, 58, 72, 73</sup> These cycles of recurrence for influenza A and B, projected back to 1920, will account for each year in which there has been an excess mortality from pneumonia and influenza — a criterion that Collins<sup>21</sup> has employed to indicate the occurrence of epidemic influenza. If the cycles are correctly defined, twelve of the eighteen epidemics of influenza since the pandemic of 1918 and 1919 have been due to influenza virus A. Seven of the twelve epidemics have been separated by two-year intervals, and the remainder by three-year intervals. Similarly, influenza B has recurred at four-year intervals three times and at five-year to six-year intervals on two occasions.

It thus appears possible to predict the probability of recurrence of influenza A or B in the United States within the definite time limits of two to three years and four to six years, respectively. Further observations in the coming years are necessary to test the validity of this theory, particularly in view of the apparent capacity of influenza virus A to undergo what might be termed "antigenic mutation." If the behavior proves to be constant, there appears to be little reason to immunize with influenza virus A in the year following an epidemic of influenza A, or with virus B in the three years following an outbreak of influenza B.

## INFLUENZA-VIRUS VACCINE

Prior to the war, several extensive studies of the prophylactic effect of influenza-virus vaccines were carried out.<sup>74-77</sup> The vaccines employed consisted of emulsions of chick-embryo tissue containing relatively low concentrations of influenza virus A. The results obtained with this vaccine indicated in general a reduction in attack rate of approximately 50 per cent in the immunized population groups.

With the development of the improved methods for growing and concentrating the viruses and the advent of war, added impetus was given to the evaluation of immunization procedures. The Commission on Influenza<sup>78, 79</sup> observed approximately 70 per cent protection during the 1943 epidemic of influenza A in immunized, as contrasted with control groups observed at California, Iowa, Michigan, Minnesota and New York. In the 1945-1946 outbreak of influenza B, the results suggested even better prevention.<sup>80, 79</sup> During the recent 1946-1947 outbreak of influenza A, however, vaccinated and control groups showed no significant difference in the occurrence of influenza,<sup>49, 80, 79a</sup> indicating the failure of the vaccine to induce immunity. In retrospect, it appears probable that this failure was due to the antigenic differences between the strain of virus responsible for the epidemic and the strains incorporated in the vaccine employed.<sup>49, 80, 79a</sup>

Although there is no reason to discount the former successful trials of immunization because of last year's failure, it is apparent that further investigation is necessary before influenza-virus vaccine is accepted as an established agent for immunization. It is possible that antigenic variations in the influenza viruses will prevent successful immunization unless new strains can be isolated from sporadic cases in advance of the epidemic and incorporated in the vaccine. There is also reason to believe that the parenteral inoculation of killed virus may not be the final answer to the prevention of influenza. Whereas such inoculation, in the majority of cases, will elevate the antibody level in the blood, the exact relation between humoral antibodies and resistance to infection is still undetermined. The portal of entry of the virus is the respiratory tract, and the possibilities of local tissue immunization, which Burnet<sup>81</sup> has emphasized, have not been exhausted.<sup>81</sup> In this regard, the experiments of McLean, Beard and Beard<sup>48</sup> with swine influenza, which in its uncomplicated form closely resembles human influenza clinically and immunologically, are pertinent. Parenteral administration of formalin-inactivated, purified swine influenza virus conferred resistance on 37 per cent of the animals to challenge infection with active virus, whereas exposure to active virus, regardless of the severity of resulting disease, rendered 82 per cent of the animals immune to subsequent infection. Such a difference is suggestive of a mechanism of immunity other than that

induced by the parenteral inoculation of virus. It is entirely possible that the virus-inactivating substances present in nasal secretions<sup>82, 83</sup> and tissue alterations in the respiratory tract following infection<sup>84-86</sup> are important factors in the mechanism of resistance.

## PANDEMIC INFLUENZA

The cause of the disastrous world-wide pandemics of influenza is not known, nor is there any sound basis for predicting when another pandemic may occur. Certainly, the epidemiologic behavior of pandemic influenza has been quite different from that of the more frequent outbreaks of influenza A or B, and the incidence of severe bacterial complications has been much higher. It seems probable that the primary inciting agent in pandemics is a virus, but whether that agent is a particularly virulent variant of influenza virus A or B or an entirely new virus, or both viruses A and B acting simultaneously, is an open question. It is also possible that pandemics result from the synergistic action of an influenza virus and one or more of the pathogenic bacteria of the respiratory tract. Whatever the cause, the discovery of the sulfonamide drugs and the antibiotic agents has provided more effective weapons for combating the deadly aspects of a pandemic — the secondary bacterial complications — than were ever available in the past.

The electron micrographs reproduced above were obtained through the kindness of D. G. Sharp, Ph.D. of Duke University School of Medicine, and J. W. Beard, M.D.

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## MASSACHUSETTS MEDICAL SOCIETY

## PROCEEDINGS OF THE COUNCIL

Stated Meeting, October 1, 1947

A STATED meeting of the Council was called to order by the president, Dr Edward P Bagg, Hampden, on Wednesday, October 1, 1947, at 10.30 a m in John Ware Hall, 8 Fenway, Boston. Two hundred and twenty-nine councilors (Appendix No 1) were present.

After opening the meeting the President read the following obituaries

**WALTER PRENTICE BOWERS** — Since the May meeting of the Council the life of Walter Prentice Bowers which lacked but eight years of spanning a century, came to a peaceful end. Perhaps he will be remembered best as an outstanding example of the practitioner of medicine. For his accomplishments as such at the age of eighty he was granted an honorary degree of Master of Arts by Harvard University his Alma Mater in medicine.

Clinton Massachusetts more specifically will remember Walter Bowers as the home town boy, son of the Baptist minister who made good entirely on his merits as a beloved physician, and as a leading citizen who among other civic activities founded the Clinton Hospital and served as president for half a century.

He served his state as well on the Board of Registration in Medicine, acting as secretary for nearly a decade. He did much to maintain and improve standards of medical practice in this capacity.

To Dr Bowers the Massachusetts Medical Society must stand forever in debt because of his vision in advocating the purchase by the Society of the *Boston Medical and Surgical Journal* and for his able management in bringing that valued publication out of the shadow of bankruptcy to a solvent state and to a position of national recognition. In addition, he, the perennial councilor guided the Massachusetts Medical Society with distinction as president from 1912 to 1914 and he never once lost sight of its best interests.

Only his close friends knew of Uncle Walter a substantial though unheralded kind deeds to students and to young professional colleagues but one and all must agree that Emerson might have had Walter Prentice Bowers in mind when he wrote, "The world is upheld by the veracity of good men, they make the earth wholesome."

**ROBERT NASON NYE** — Today the *New England Journal of Medicine* enjoys a preferred status among students of medicine old and young no matter where the healing art has called them in prospect, in practice or in teaching and research, just as in wartime the accurate and authoritative information bound within the modest white covers followed them everywhere from Arctic snows to steaming tropical jungles. Already we have dealt with the passing in the fullness of years of Walter Bowers the inspired editor who laid the groundwork for this notable achievement.

By a tragic coincidence the sad duty devolves upon us to record at this same session the untimely completion of such mortal data as concern the life of Robert Nason Nye who brought to fruition the fondest dreams of his predecessor in the management of the *Journal*.

Of Robert Frost, our New England poet a wise critic wrote that, "Truth has been his central passion." The

poet himself declared that, "The fact is the sweetest dream that labor knows furthermore, in a philosophic mood he continued

And were an epitaph to be my story  
I'd have a short one of my own  
I would have written of me on my stone  
I had a lover a quarrel with the world

That is to say he held himself free to question the world, even to criticize but always with understanding and real feeling.

Such a brief summary would describe the spirit of Robert Nye as accurately as that of Robert Frost. But in addition, Bob Nye graduated from Harvard *cum laude* whereas the other Bob left at the end of two years. And though the poet managed the rock bound farm after a fashion the pathologist, turned editor, evinced so positive an aptitude for business management that credit balances have resulted for our publication. Both men of letters united their vocations and their vocations as their two eyes made one in sight. Both were sensitive observers of the world about them whether the phenomena were natural or human.

Only yesterday it seems Bob came seeking a sufficient advance to cover the purchase of next year's paper and for confirmation of the accuracy of an editorial. Today his chair stands vacant his blue pencil lying where it left his hand.

The world of medical publication will miss the exemplary work of the perfectionist, Dr Robert Nye. Likewise will the Massachusetts Medical Society feel the absence of his sound advice and cheerful co-operation in special committee work. But we who have known him and worked with him will miss still more the genial personality. We who have taken Bob Nye for granted for so long confess our deep dismay in the contemplation of replacement of this able man who met his ultimate deadline on the tenth of September.

The inspiration of lives such as these must persist and spur us on to keep our standards high and relations with our fellows human. May the "Peace that passeth all understanding reward their several labors.

At the request of the President, the Council stood for one minute in silent tribute to the memory of Dr Bowers and Dr Nye.

The Secretary presented the record of the annual meeting of the Council, held on May 19, 1947, as published in the *New England Journal of Medicine*, issue of August 21, 1947, and moved its acceptance. The motion was seconded by Dr Harold G Giddings, Middlesex South, and it was so ordered by vote of the Council.

## APPOINTMENTS

The President then announced the following interim appointments

To the Committee to Study Special Services

Dr Elmer S Bagnall Essex North and Mr Reginald F Cahalane representing Massachusetts Hospital Service

\*Untermeyer, L. Introduction and commentary. *Pocket Book of Robert Frost's Poems*. 263 pp. New York: Pocket Books, Inc., 1946. P 12

Dr Arthur W Allen, Suffolk, and Dr Charles G Hayden, Norfolk, representing Massachusetts Medical Service  
 Mr Frank E Wing, Rev Donald A McGowan and Dr Charles F Wilinsky, Suffolk, representing Massachusetts Hospital Association  
 Dr Merrill C Sosman, Suffolk, and Dr Hugh F Hare, Middlesex South, representing the specialty of radiology  
 Dr G Kenneth Mallory, Norfolk, and Dr Donald A Nickerson, Middlesex East, representing the specialty of pathology  
 Dr Urban H Eversole, Norfolk, and Dr Sidney C Wiggan, Suffolk, representing the specialty of anesthesiology  
 Dr Leland S McKittrick, Suffolk, chairman, and Dr Joseph Garland, Suffolk, secretary, representing the Massachusetts Medical Society

*To the Subcommittee on National Legislation*

Dr Charles G Hayden, Norfolk

*To the Committee on Postgraduate Medical Education*

Dr Leo F King, Middlesex North  
 Dr Claude E Welch, Suffolk.

*To the Committee on New England Postgraduate Assembly*

Dr Joseph Garland, Suffolk

*To the Committee to Survey Salaries*

Dr Albert A Hornor, Suffolk

*As Advisory Council to the Woman's Auxiliary of the Massachusetts Medical Society*

Dr John F Conlin, Suffolk, chairman  
 Dr Milton J Quinn, Middlesex East  
 Dr David L Belding, Norfolk South

*To the Committee on School Health*

Dr Kenneth L MacLachlan, Middlesex East

*Delegates (June 1, 1947, to June 1, 1949)\**

DELEGATES	ALTERNATES
Dr Charles J Kickham, Norfolk	Dr John Fallon, Worcester
Dr Leland S McKittrick, Suffolk	Dr Harold R Kurth, Essex North
Dr Patrick J Sullivan, Berkshire	Dr Allen G Rice, Hampden

*Delegate to Annual Meeting of the Vermont State Medical Society*

Dr Wilfred T Hood, Middlesex South

*To Annual Meeting of House of Delegates of the American Medical Association, June, 1947*

Dr Allen G Rice, Hampden

*To the Council*

Dr Walter L Sargent, Norfolk South, to replace Dr Reardon, *ex-officio*  
 Dr Robert S Palmer, Norfolk, to replace Dr Kickham, *ex-officio*  
 Dr Carl F Maraldi, Suffolk, to replace Dr Garland, *ex-officio*  
 Dr Leland S McKittrick, Suffolk, to replace Dr Nye, deceased

*Delegates to Veterans Administration Home Town Medical Care Program, November, 1947*

Dr Humphrey L McCarthy, Norfolk  
 Dr James K Bragger, Norfolk

*To the Veterans Administration Board of Review*

Dr Humphrey L McCarthy, Norfolk  
 Dr James K Bragger, Norfolk  
 Dr Timothy F P Lyons, Norfolk  
 Dr Edward P Bagg, Hampden  
 Dr Joseph Garland, Suffolk

The President asked for confirmation of these appointments, and it was so ordered by vote of the Council

REPORTS OF COMMITTEES

*Executive Committee* — Dr Joseph Garland, Suffolk, Secretary

The Secretary submitted the report (Appendix No 2) as distributed in mimeographed form and moved its acceptance. It was so ordered by vote of the Council

*Committee on Membership* — Dr Peirce H Leavitt, Plymouth, Chairman

This report had been distributed to the Executive Committee in mimeographed form and accepted by that committee with one amendment, as set forth in the report of the Executive Committee. Dr Leavitt moved the acceptance of the report, the motion was seconded and it was so ordered by vote of the Council

*Committee on Public Relations* — Dr Harold R Kurth, Essex North, Secretary

This report (Appendix No 3) was submitted by the President, who pointed out that the chief subject of contention in the report had to do with the Blue Shield policyholders' status as regards income. Dr H M Kemp, Franklin, had indicated that little attempt was being made by Blue Shield to determine accurately an applicant's yearly income. Often a physician, aware that his patient's income is above the accepted \$3000, is entitled to make extra charges, but finds that he cannot do so because the patient has been issued an unlimited instead of a limited policy.

Dr N S Scarcello, Worcester, had offered the following resolution: "That the Blue Shield through its employees determine accurately an applicant's yearly earnings before issuing the policy, and secondly, that these earnings be reviewed each year." This resolution had been adopted by the Committee on Public Relations.

The Executive Committee recommended that the Council refer this matter back to the subcommittee appointed to investigate the relations between members of the Massachusetts Medical Society and the Blue Cross and Blue Shield, for further study and conference with Dr Charles G Hayden, medical director of the Blue Shield and Blue Cross.

In order that the matter might be discussed clearly and authoritatively the President had invited Dr Charles G Hayden and Dr James C McCann, president of Blue Shield, to attend this meeting of the Council. Dr Bagg asked the Council, therefore, to give unanimous consent to Drs Hayden and McCann to speak on the question. This consent was granted.

\*Advance necessitated by midyear meeting of House of Delegates of American Medical Association

Dr N S Scarcello, Worcester, spoke against returning the question to the committee, arguing strongly in favor of his original resolution adopted by the Committee on Public Relations that Blue Shield ascertain an applicant's yearly earnings and review them yearly. He then moved the adoption of the resolution. The motion was seconded.

Dr James C McCann, in discussing the resolution, mentioned the original close integration between the Council of the Society and the Blue Shield, which the Council had created — an integration that was apparently now lacking. He spoke at length on the difficulties of determining the income level that should separate limited from unlimited policies, and the difficulties and the cost of frequent appraisal of policy holders' incomes.

Dr Charles G Hayden indicated the economies that Blue Cross and Blue Shield are establishing in cutting their payrolls, thereby effecting savings that can be used for increased benefits to subscribers and to accumulate proper reserves as required by the Commissioner of Insurance.

Dr Elmer S Bagnall, Essex North, called attention to the fact that each district has a professional service committee established under the by-laws of the Blue Shield, and that in the Blue Shield is a central professional service committee. Each district has also a district administrative committee.

Dr James P O'Hare, Suffolk, agreed with Dr Scarcello that the responsibility for determining the income of subscribers is not one that the physicians should assume.

After further discussion by Drs John Fallon, Worcester, J J Curley, Worcester North, Charles G Hayden, James C McCann, C C Lund, Suffolk, and Frank R. Ober, Suffolk, Dr Harold R Kurth, Essex North, offered an amendment to Dr Scarcello's resolution by suggesting that the whole problem of the question of income be referred back to the Subcommittee on Blue Cross and Blue Shield Problems of the Committee on Public Relations for further study after consultation with Dr Charles G Hayden. The motion was seconded by Dr Bagnall, Essex North. Dr Scarcello raised as a point of order the fact that the amendment controverted the resolution.

The point of order being upheld, the original motion was put to vote and failed of passage.

On motion of Dr M Fremont-Smith, Suffolk, seconded by Dr F R Ober, Suffolk, the question was referred back to the committee for further study.

The President then called attention to the fact that establishment of a Woman's Auxiliary was under way, as reported to the Committee on Public Relations by Dr Milton J Quinn, Middlesex East.

On motion of Dr J V McHugh, Worcester North, duly seconded, the report of the Committee on Public Relations was accepted by the Council as one of information only.

#### *Committee on Legislation — Dr George R Dunlop, Worcester, Chairman*

This informational report, which is as follows, was presented by Dr Dunlop.

Since the last meeting of the Council the Committee on Legislation met and authorized Dr Elmer S Bagnall to represent the Massachusetts Medical Society during the hearings on the Taft-Smith-Ball-Donnell Bill (S 545) before the Subcommittee of the Senate Committee on Labor and Public Welfare. During the summer Dr Bagnall called the Subcommittee on National Legislation together for a study and discussion of S 545 preceding his testimony before the Senate Committee. The bill was evaluated and measured by the basic principles governing medical-care plans as published by the Massachusetts Medical Society on February 6, 1946. It was recommended that greater emphasis be placed upon public health and community preventive medicine, a larger appropriation be allocated for research greater powers be given to all advisory councils and partial aid to those who could pay in part for their medical care be eliminated.

On Wednesday June 4, 1947, Dr Bagnall testified before the Subcommittee on Labor and Public Welfare to the effect that the Massachusetts Medical Society favored the ultimate creation of a federal Department of Health at cabinet level, headed by a physician. In the light of the principles adopted by the Society for governing medical care plans he showed that S 545 had certain strengths and certain weaknesses. Recommendations were made for clarification and strengthening the provisions in this bill. A copy of Dr Bagnall's testimony is available under the reports of the hearings on this legislation.

On June 5 1947 the Senate Committee on Expenditures in the Executive Departments agreed to report on S. 140, as amended. It was the opinion of the Subcommittee on National Legislation of the Society that "if federal activities in the field of public health are to be elevated to cabinet level, they should not be combined with education, security or any other field." Senator Taft, himself believed that health was too important to be combined with welfare and education.

Congress adjourned without any action on the bill and as the Social Security Board is to be investigated favorable action on the bill in its present form seems unlikely.

House Bill 705 which later became House Bill 1921 was finally rejected by the Massachusetts House of Representatives on June 19, 1947. This bill prohibited the employment in schools of persons suffering from tuberculosis in communicable form and provided for periodic examination of school employees.

House Bill 274 providing for an appointment of a special commission to investigate and study the public-health laws and policies of the Commonwealth was combined with H 1870 and H 2137 to become H 2338. This latter was enacted and signed by the Governor on June 30 1947.

It might be important to note that during the year 1947-1948, all petitions to come before the General Court must be filed on or before the first Wednesday in December. Petitions after this date will have to come before the Rules Committee.

Dr Dunlop moved the acceptance of the report, the motion was accepted, and it was so ordered by vote of the Council.

#### *Committee on Arrangements — Dr G Guy Bailey, Jr, Middlesex South, Chairman*

This informational report, which is as follows, was presented by the President in the absence of Dr Bailey.

The Committee on Arrangements reports that it has selected the dates of May 25 26 and 27 1948 for the annual meeting of the Society and has selected the Hotel Statler in Boston as the place of the meeting.

It is the plan of this committee to try to encourage more and better scientific exhibits at next year's meeting, and a section of the foyer has been set aside for this purpose

Dr A A Hornor, Suffolk, moved the acceptance of the report. The motion was seconded, and it was so ordered by vote of the Council

*Committee on Finance*—Dr Robert W Buck, Suffolk, *Chairman*

This report, which contains two recommendations, was presented by Dr Buck as follows

The Committee on Finance has approved additional expenditures amounting to \$300 to cover the cost of dinner meetings of two committees

The Finance Committee has also voted to approve the suggestions made by the treasurer of the Society, Dr Eliot Hubbard, as found in the report of the Executive Committee of the Council, February 5, 1947. Dr Hubbard suggested that if the annual dues were raised to \$25 00, he would like to make the following recommendations

"1 That the refund to district societies be increased from \$4000 a year to \$8000"

The Committee on Finance approves this suggestion and recommends its adoption

"2 That the total amount of the assets of the General Fund be set at \$250,000, and not be increased each year by reinvestment of surplus, and that in any given year, after running expenses have been paid and aid to the Boston Medical Library and other beneficiaries given, the balance of income over expenditures be automatically turned over to the Building Fund. This fund so augmented would assure the purchase of adequate headquarters at the proper time and would allow for a Building Fund endowment, the income from which would support the running of this establishment"

The Finance Committee approves this suggestion and recommends its adoption

Dr Buck moved the acceptance of the report as a whole. The motion was seconded, and it was so ordered by vote of the Council

Dr Buck then moved the adoption of the first recommendation, which is that the refund to district societies be increased from \$4000 to \$8000 yearly, after the annual dues have been increased. The motion was seconded, and it was so ordered by vote of the Council

Dr Buck moved the adoption of the second recommendation as printed above. The motion was seconded and it was so ordered by vote of the Council

*Committee on Cancer*—Dr Shields Warren, Suffolk, *Chairman*

This report, which contains one recommendation, was presented by Dr Allen G Rice, Hampden, and is as follows

The Palmer Memorial Unit of the New England Deaconess Hospital has asked approval of the Suffolk District Medical Society for the establishment of a Cancer Detection Clinic. In view of the special character of the problem this request was turned over to the Committee on Cancer by the Suffolk District Medical Society

The Committee recommends that the request of the New England Deaconess Hospital for the establishment of a Cancer Detection Clinic be approved

It is well for members of the Society to be aware of the wide opportunities that exist for funds for cancer research and for cancer education. The United States Public

Health Service has made available to each approved medical school a sum up to \$25,000 for the teaching of cancer. The budget of the United States Public Health Service approved by the last Congress carried a \$14,000,000 item for work in the field of cancer, chiefly along the lines of education and research

The Massachusetts Division, Inc., of the American Cancer Society has raised approximately \$358,000 this year, and the American Cancer Society in its nation-wide campaign has raised \$11,500,000. The grants made in the Commonwealth by the national society have been chiefly on a research-grant basis, and hence, largely restricted to metropolitan areas. The Massachusetts Division, Inc., of the American Cancer Society has a much more intimate knowledge of the situation that exists within the state, and consequently has been able to make a far wider distribution of its funds. Support of research, service or education has been carried out in the following communities: Boston, Brockton, Brookline, Cambridge, Fall River, Lowell, Pittsfield, Springfield, Westfield, Worcester and Wrentham

Dr Rice moved the acceptance of the report as a whole. The motion was seconded by Dr F R Ober, Suffolk. Dr Bagg then asked the consent of the Council to permit Dr Clifford C Franseen to discuss the proposed Cancer Detection Clinic and answer any questions that councilors might have concerning it. This consent was unanimously granted

Dr Franseen explained that according to recommendations of the American Cancer Society and the American College of Surgeons, the approval of the County Medical Society must be obtained before such a clinic is established. In this instance, because of a special situation, the Suffolk District Society had turned the request over to the Committee on Cancer, which presented it to the Council for approval. The special situation was that the Massachusetts Department of Public Health had funds available from a federal grant to subsidize this clinic for cases in which the patient could not pay the full fee

In the discussion that followed it became apparent that the Council was not convinced that the organization of the clinic had yet reached a stage where the Council was ready to give its approval

Dr N S Scarcello, Worcester, moved that the recommendation be tabled until the plans for the clinic had been completely worked up, when it could be reintroduced to the Council. This motion was seconded, and it was so ordered by vote of the Council

*Committee on Physical Medicine*—Dr Arthur L Watkins, Middlesex South, *Chairman*

This report, which contains three recommendations requested by the Massachusetts Department of Education regarding establishing standards of training and education in the field of physiotherapy, was presented by Dr Watkins and is as follows

This committee, on April 30, 1947, had referred to it by Dr John F Wostrel, supervisor of private trade schools, Department of Education, Commonwealth of Massachusetts, a request for aid in establishing standards of training and education for the teaching staffs of licensed

private trade schools in the field of physiotherapy. These schools are not approved by the American Medical Association and do not operate on the level required by the American Medical Association.

In reply to this request the following recommendations are made:

1 The technical director of a school of physical therapy should be certified by the American Registry of Physical Therapy Technicians and have a minimum of five years' experience as a physical therapist, working in clinics or hospitals employing other registered physical therapists.

2 Assistant directors or instructors should be certified by the American Registry of Physical Therapy Technicians and have two years' experience in a hospital or clinic employing other registered physical therapists.

3 It is further recommended that the minimum requirement for entrance to all licensed trade schools in the field of physical therapy (physiotherapy) include two years of college with courses in the basic sciences or in case high school graduates are admitted, there should be a minimum of two academic years of college level including courses in basic sciences.

Dr Watkins moved that the recommendations as published be adopted. The motion was seconded by Dr Bagnall, and it was so ordered by vote of the Council.

Dr Watkins then moved the acceptance of the report as a whole. The motion was seconded by Dr Bagnall, and it was so ordered by vote of the Council.

*Committee to Meet with General Hawley* — Dr Humphrey L. McCarthy, Norfolk, *Chairman*

This informational report (Appendix No. 4), containing the agreement entered into between the Massachusetts Medical Society and the Veterans Administration in accordance with the Kansas Plan, was presented by Dr Bagg in the absence of Dr McCarthy.

The acceptance of this report and the approval by the Council of a board of review to be nominated by the President according to Section 9 of the agreement were moved by Dr Hornor. The motion was seconded by Dr Ober and it was so ordered by vote of the Council.

*Committee to Survey Malpractice Insurance in Massachusetts* — Dr Carl Bearse, Norfolk, *Chairman*

This report (Appendix No. 5), which contains four recommendations, was presented by the chairman, who moved the adoption of the first recommendation, that the Massachusetts Medical Society should not undertake its own liability insurance at this time.

The motion was seconded by Dr Hornor, and it was adopted by vote of the Council.

Dr Bearse moved the adoption of the second recommendation, that no one insurance company be recommended exclusively at this time. The motion was seconded by Dr Ober, and it was adopted by vote of the Council.

Dr Bearse then moved the adoption of the third recommendation, that a special committee of five fellows be appointed by the President to act in an

advisory capacity to the Society and insurance companies in regard to malpractice insurance. The motion was seconded by Dr Bagnall, and after some discussion it was so ordered by vote of the Council.

Dr Bearse moved the adoption of the fourth recommendation, that the present committee be discharged. This motion was seconded by Dr Hornor and was adopted by vote of the Council. Dr Bearse then moved the acceptance of the report as a whole, the motion was seconded, and it was so ordered, with thanks, by vote of the Council.

*Committee on New England Postgraduate Assembly* —

Dr Leroy E. Parkins, Suffolk, *Chairman*

This report, of progress only, was presented by the chairman and is as follows:

The Committee invited the other New England state medical societies to participate in organizing an assembly all accepted and appointed members to a joint executive committee.

A program committee was appointed representing all the societies; the program is being published in the *Journal*, and a copy will be mailed to each registered physician in New England.

The Assembly will be held October 29 to 31, 1947.

Dr Parkins moved its acceptance. This motion was seconded by Dr Hornor, and it was so ordered by vote of the Council.

*Committee to Establish a Pension Plan* — Dr Robert W. Buck, Middlesex South, *Chairman*

This report (Appendix No. 6) was presented by the chairman.

In offering the report, Dr Buck stated that the committee wished to amend its recommendations so that a pension of 50 per cent of the salary at the time the insurance is written, instead of the average salary, be provided as a goal. If the recipient is granted increase in wages between the time he becomes eligible and the time he reaches the retirement age, proportionate increases in benefits must be added to the terms of the policy, but in no case, irrespective of the age at the time the policy is written, is the final monthly pension payment to be more than \$200.

Dr Buck then moved the adoption of the recommendation as amended, the motion was seconded by Dr Chapin and it was so ordered by vote of the Council.

Dr Buck moved the acceptance of the report as a whole, the motion was seconded and it was so ordered by vote of the Council.

*Advisory Committee on School Medical Services* — Dr Stewart H. Clifford, Middlesex South, *Chairman*

This report (Appendix No. 7) was offered by the President. After some discussion of the difficulties that the Committee had encountered in its deliberations, Dr Bagnall moved that the recommendation of the Executive Committee that the report



be referred back to the committee for further study be adopted. The motion was seconded and it was so ordered by vote of the Council.

*Report of the Massachusetts Representatives to the House of Delegates of the American Medical Association*

This report (Appendix No. 8) prepared by Dr. David D. Scannell, Norfolk, was submitted by the President. Its acceptance was moved by Dr. Hornor, the motion was seconded, and it was accepted by vote of the Council.

*Committee to Study Special Services — Dr. Leland S. McKittrick, Suffolk, Chairman*

The report of this committee (Appendix No. 9) was read by the Secretary. Its acceptance was moved by Dr. Hornor and seconded by Dr. Ober.

Dr. George L. Schadt, Hampden, in discussion, moved that a preamble be attached to the report designating it as an interim report until it could be more fully studied by the societies of radiologists, pathologists and anesthetists, and a final agreement reached.

In the course of the discussion that followed, Dr. Bagg made it clear that the above-named societies, the hospital associations, the Blue Cross and the Blue Shield were represented on the committee, and that the committee was unanimously behind the report.

After further discussion the amendment was put to vote and was not accepted, and the report, being put to vote, was unanimously accepted by the Council, and the committee was discharged.

The Secretary read a communication from Mrs. Robert N. Nye, expressing her appreciation for the flowers that had been sent in the name of the Society to Dr. Nye's funeral services. He went on to tell of the gifts of money that had been received by the Massachusetts Division of the American Cancer Society in memory of Dr. Nye, in lieu of flowers, and of the opportunity that existed of adding to this memorial fund.

#### NEW APPOINTMENTS

The following new appointments were then offered by the President and were confirmed by vote of the Council.

*To the Advisory Committee on Malpractice Insurance*

Dr. Carl Bearse, Norfolk, Chairman  
Dr. William J. Brickley, Suffolk  
Dr. Maurice Fremont-Smith, Suffolk  
Dr. Guy L. Richardson, Essex North  
Dr. Horatio Rogers, Suffolk

*To the Committee of Seven*

Dr. Reginald Fitz, Suffolk, Chairman  
Dr. Frank B. Carr, Worcester  
Dr. W. A. R. Chapin, Hampden  
Dr. Lawrence R. Dame, Franklin  
Dr. Peirce H. Leavitt, Plymouth  
Dr. Dwight O'Hara, Middlesex South  
Dr. Walter G. Phippen, Essex South

#### NEW BUSINESS

The following letter to the President was read by the Secretary.

Dear Dr. Bagg,

There is one matter in connection with my administration as president of the Massachusetts Medical Society, that I feel has been left in the category of unfinished business, and I feel that I should call it to your attention specifically on this account.

The matter of establishing the secretaryship of the Society on a full-time basis was discussed frequently at the meetings of the Committee of Seven during 1945 and 1946. It was brought before the Council by Dr. Ober's special committee and accepted in principle at the meeting of February 5, 1947. You will remember that we talked it over before you approached Dr. Tighe on the subject the last time he was at the society headquarters. In spite of all this priming, somehow there did not seem to be a suitable way to bring it before the Council at the annual meeting and so it has gone on.

My feeling that we need a full-time secretary is very strong and my experience during the period of Dr. Tighe's illness and absence confirms this feeling in a most conclusive manner. There are, furthermore, matters which should be kept on record in connection with the annals of the Society which have been and are being forgotten every day. Dr. Burrage's history stopped twenty-five years ago and it seems to me that the activities of the Society during the past quarter-century transcend all previous work and should be recorded before our generation completely passes away. I furthermore believe there is a vital need for more accounts of the work of the thirty-odd committees of the Society to be published in the *New England Journal of Medicine* because it is only by such publication that the fellows as a whole have an opportunity to know what is being done and what is being thought. There are, of course, other reasons with which I know you are familiar.

The real purpose of my writing this letter is to place formally in your hands my belief in the need and my hope that some way may be worked out for the action which will lead to the suitable arrangement for a full-time secretary for the Massachusetts Medical Society.

With all good wishes, I am

DWIGHT O'HARA, M.D.

Dr. O'Hara, after a few explanatory remarks, moved that the President be asked to nominate a Committee of Seven to consider the matter of a full-time secretaryship, with power to act, to report to the Council at its next meeting. Dr. Fremont-Smith seconded the motion. Dr. Hornor offered as an amendment, which was accepted by Dr. O'Hara, that the committee also have the power to determine the salary it might offer.

Dr. Bagg suggested that the committee should also define the fields of Secretary and Executive Secretary and Director of Information so that there will be no overlapping of functions.

The question was put to vote and the motion was accepted by the Council.

The following letter to the President was then read by the Secretary.

Frequent calls for the recommendation of names of physicians for the treatment of patients throughout the state continue to come into the main office of the Society.

In our experience the present method of referring such inquiries to the secretary of the proper district society is cumbersome and too dilatory.

Hence, I would like to suggest that the matter be reopened and referred once more to the appropriate committee for further study in order to provide better service to the public.

JOSEPH GARLAND, M.D., Secretary

As recommended by the Executive Committee, this matter was referred to the Committee on Public Relations by vote of the Council.

The following communication from the trustees of the Boston Medical Library was read by the Secretary for purposes of information.

Dear Dr. Garland

As secretary of the Boston Medical Library I acknowledge with great pleasure your letter dated June 1, 1947, informing me of the action taken by the Council of the Massachusetts Medical Society with respect to the Boston Medical Library.

In accordance with this action, the Trustees of the Boston Medical Library have voted to propose changes in their by-laws to be acted upon at a special meeting of the Corporation on November 17, 1947, whereby a new class of membership in the Boston Medical Library to be known as Massachusetts Medical Society Member will be created. Any non-resident fellow of the Massachusetts Medical Society, active or retired as long as he remains in good standing after January 1, 1948, will automatically be in this class. He will be given the same privileges as other members, including of course, the taking out of books and periodicals. Another change in the by-laws which has been proposed will be the addition of four trustees to be appointed by the Massachusetts Medical Society. A copy of these revised by-laws will be sent to you after their adoption by the Corporation.

It is hoped that in this way a closer co-operation of the activities of the Massachusetts Medical Society and the Boston Medical Library will be effected.

BENJAMIN CASTLEMAN M.D. Secretary

Dr. L. E. Parkins, Suffolk, offered the resolution that the Committee on Postgraduate Assembly be directed to enter into discussions with the Assembly representatives of the other New England states, as well as with the Council of New England state medical societies, for the purpose of setting up an organization to carry on the future work of the Assembly, and that after such an organization had been agreed upon by the committee it be reported to the Council for final approval.

The resolution was seconded and was accepted by vote of the Council.

The following communication was read by the Secretary, who moved its referral to the proper committee.

The accompanying letter concerns a special project for the medical care of children of veterans at Harvard University. This matter was presented to me during the summer as one approved by the State Department of Public Health and a plan about to be placed in operation with the opening of the school year.

The sponsors have shown every effort to obtain the approval of the Massachusetts Medical Society in advance of the plan's operation. This has not been possible under our By-Laws.

I offer this matter as an item of new business for referral for study by the appropriate committee. I will be at the service of the committee for whatever additional information it may require.

JOHN F. CONNOR M.D.

Director of Medical Information and Education

Dear Dr. Conlin

This letter is to confirm our telephone conversation relative to obtaining official approval by the Massachusetts Medical Society of a special project for the care of children of veterans at Harvard University.

During the past winter several medical problems arose among the children of veterans at Harvard that gave

cause for concern by those in medically responsible positions at Harvard and at Harvard Deacons Village.

The veteran students in general were on small government stipends not allowing for adequate medical care for their children. Arlie V. Bock, M.D. requested Allan N. Butler M.D. to see if he could devise some means whereby such care could be provided. Dr. Butler consulted Gerald N. Hoeffel M.D., Dorothea M. Moore M.D., and Ralph A. Ross M.D. pediatricians of Cambridge who were caring for many of the children in this area and Al Weller M.D. of Arlington who was caring for a group at Harvard Deacons. These physicians confirmed the need of some type of medical aid and indicated that they were carrying a heavy case load without adequate compensation for services rendered. Inquiries indicated that Government funds could be made available from the Children's Bureau via the Massachusetts Department of Public Health via the State Division of Maternal and Child Welfare, provided it be done as a study as well as a service project.

The request for such funds was submitted as follows.

The purpose of this project is to give medical care for children of G. I.'s who are on small Government stipends at Harvard and at Fort Devens. These students come from many states other than Massachusetts. There will be no economic or racial determination of eligibility and no other limiting factor. It will be sponsored by Massachusetts General Hospital. The Child Health service will notify the G. I. students concerning the availability of the service and will give them exact information as to how to secure this service.

The service to these children will be given through child health conferences, pediatric and consultation service in the home, out patient care at the Massachusetts General Hospital and hospital medical and surgical care at the Massachusetts General and other qualified hospitals. The special diagnostic and treatment services at the Massachusetts General will be available to this child health service. The Massachusetts General Hospital provides unusually good facilities staffed by personnel with the highest professional qualifications and used as a teaching hospital by the Harvard School of Public Health. It is licensed by the Massachusetts Department of Public Health. Harvard University will furnish office space at Harvard and conference space and facilities both in Cambridge and at Fort Devens.

Consultation service in the homes will be given through practicing pediatricians who are licensees of the American Board of Pediatrics. The cost will be \$10.00 per home visit.

All physicians will be licensed to practice in Massachusetts. There will be also a part time medical director.

He will be a senior pediatrician who is a licensee of the American Board of Pediatrics, a member of the Staff of the Children's Medical Service, Massachusetts General Hospital and a member of the Department of Pediatrics of Harvard or Tufts University.

The two full time pediatricians will be graduates of a Grade A medical school and will have had an internship and one or more residencies which meet the qualifications of the American Board of Pediatrics.

Consultants will be physicians who are licensees of the American Board covering their particular field of specialty.

The public health nurses meeting the qualifications of the supervisory nurse of the Massachusetts Department of Public Health will be employed under the supervision of the Bureau of Public Health Nursing of the Massachusetts Department of Public Health. They will do generalized service for the entire family.

Nutrition and medical social consultation will be available through the Massachusetts Department of Public Health.

Consultation service will also be available through the Division of Maternal and Child Health.

Two full time clerks will be employed.

There are at present, at Harvard, 1412 children of G I's. This total number will increase during the year due to approximately 350 pregnancies. Therefore, we base our request for funds on 1500 children at a cost of \$35.00 per child.

The operation of this service provides an excellent opportunity for statistical analysis of this type of care and for study of administrative problems. For this purpose, a principal statistical clerk, a statistical machine operator and rental of statistical machine, equipment and supplies are essential. The Harvard School of Public Health will participate in the statistical analysis of this type of care and in study of administrative problems. The cost of such analysis is budgeted separately from the cost of providing the actual health and medical care.

Quarterly reports of services rendered will be made to the Division of Maternal and Child Health covering the number of children receiving each type of service including attendance at well child conferences, home visits, consultant visits in the home, number of outpatient visits and number of hospital days' care per child, with diagnosis and types of treatment. These forms will be submitted when available.

There is every reason to believe that there will be the same need of child health services next year. A request to continue this service should, therefore, be anticipated.

The funds were made available to the State of Massachusetts to be administered by the Massachusetts General Hospital. Harvard University has agreed to supply office and clinic space and will furnish both with such furniture as is appropriate for the needs of the project.

At conferences held with representatives of the Children's Bureau of the State Division of Maternal and Child Health and with representatives of Cambridge public-health services it has been emphasized that official approval of the medical profession be obtained before proceeding further.

FRANCIS C. McDONALD, M.D.

The motion was seconded and carried, and the communication was referred by the President to the Committee on Medical Education.

The following communication was read by the Secretary, who moved its referral to the proper committee.

Dear Dr. Garland:

I am writing to bring the following matter to the attention of the Officers and Council of the Massachusetts Medical Society.

The Committee on Fetus and Newborn of the American Academy of Pediatrics is working out a program to improve the facilities for the care of newborn infants which will include medical, nursing and hospital care, medical social services and the need for training of personnel.

In an effort to activate this program at the State and eventually at the local level, Dr. Stewart H. Clifford, the Chairman of the Committee, with the approval of the Executive Board of the Academy, has requested the State Chairmen to appoint a State committee on Fetus and Newborn. Dr. Clement A. Smith has agreed to act as chairman of such a committee in Massachusetts. Eleven other physicians interested in this problem have been invited to serve on the committee.

The program developed by the National Committee will be presented in detail at the annual meeting of the American Academy of Pediatrics on December 8, 1947, in Dallas, Texas. It is hoped that the Massachusetts committee will begin to function after that time and that eventually there will be local committees to carry out the details of the program in the state.

It is the intention of the American Academy of Pediatrics that this program be carried out with the approval and co-operation of the State Medical Societies.

JAMES MARVIN BATY, M.D.  
State Chairman for Massachusetts,  
American Academy of Pediatrics

This motion was seconded and carried, and the communication was referred by the President to the Committee on Medical Education.

Dr. B. C. Wheeler, Worcester, then proffered the following invitation from the Worcester District Medical Society:

Mr. President, on behalf of the Worcester District Medical Society, I should like to present a cordial invitation to hold the 1949 annual meeting of this Society in Worcester. It will then have been eleven years since the last annual meeting in Worcester and the Worcester District Medical Society would consider it an honor and a privilege to act as host again. This is pursuant to a unanimous vote of the regular monthly meeting of our District Society held on September 10, 1947.

Dr. O'Hara moved that the invitation be accepted with gratitude and referred to the Committee on Arrangements. This motion was seconded by Dr. Hornor, and it was so ordered by vote of the Council.

There being no further business before the Council, the President announced it adjourned at 1:50 p.m.

JOSEPH GARLAND, Secretary

APPENDIX NO. 1

ATTENDANCE OF COUNCILORS

BARNSTABLE	G. L. Richardson
P. P. Henson	F. W. Snow
J. G. Kelley	
J. I. B. Vail	ESSEX SOUTH
	Bernard Appel
BERKSHIRE	W. W. Babson
Helen M. Scoville	L. F. Box
P. J. Sullivan	S. E. Goulding
E. R. Wyman	C. A. Herrick
	W. R. Irving
BRISTOL NORTH	P. P. Johnson
J. V. Chatigny	A. E. Parkhurst
W. E. Dawson	W. G. Phippen
M. E. Johnson	E. D. Reynolds
J. L. Murphy	H. D. Stebbins
W. M. Stobbs	P. E. Tivnan
	C. F. Twomey
BRISTOL SOUTH	FRANKLIN
G. W. Blood	L. R. Dame
R. B. Butler	
E. D. Gardner	HAMPDEN
R. H. Goodwin	F. A. Allen
William Mason	E. P. Bagg
H. E. Perry	R. L. Barrett
C. C. Tripp	W. A. R. Chapin
Henry Wardle	E. C. Dubois
ESSEX NORTH	A. F. G. Edgelow
H. M. Allen	Frederic Hagler
E. S. Bagnall	G. D. Henderson
R. V. Baketel	Charles Jurist
G. J. Connor	R. T. Miller
Elizabeth Councilman	A. G. Rice
H. F. Fenton	A. H. Riordan
H. R. Kurth	G. L. Schadt
P. J. Look	J. A. Seaman
L. C. Peirce	HAMPSHIRE
	H. A. Tadgell

## MIDDLESEX EAST

J. L. Anderson  
T. P. Devlin  
Robert Dutton  
E. M. Halligan  
D. L. Joyce  
R. W. Layton  
K. L. MacLachlan  
M. J. Quinn  
R. R. Stratton

## MIDDLESEX NORTH

R. E. Cole  
W. E. Collins  
S. A. Dibbina  
A. J. Stewart

## MIDDLESEX SOUTH

E. W. Barton  
Harris Bass  
J. M. Baty  
H. K. Bloom  
G. F. H. Bowers  
Alice M. Broadhurst  
Madelaine R. Brown  
R. H. Brown  
R. W. Buck  
E. J. Butler  
J. F. Casey  
E. A. Cooney  
J. A. Daley  
J. G. Downing  
A. G. Engelbach  
H. O. Gallupe  
F. W. Gay  
V. A. Getting  
H. G. Giddings  
J. D. Golden  
Elliot Hubbard Jr.  
F. J. Joutet  
S. B. Kelley  
A. A. Levi  
A. N. Makechnie  
J. H. McSweeney  
Dudley Merrill  
C. E. Mongan  
E. J. O'Brien Jr.  
Dwight O'Hara  
Fabyan Packard  
Randolph Piper  
E. W. Small  
A. W. Stearns  
H. P. Stevens  
J. B. Townsend  
J. E. Vance  
A. L. Watkins  
B. M. Wein  
R. H. Wells  
Hovhannes Zovickian

## NORFOLK

A. A. Abrams  
C. M. Allard  
B. E. Barton  
Carl Bearse  
Elizabeth Broyles  
J. H. Cauley  
G. L. Doherty  
Albert Ehrenfried  
J. M. Faulkner  
Susannah Friedman  
D. L. Halbersleben  
H. B. Harms  
Gilbert Horrax  
P. J. Jakmaush  
I. R. Jankelson  
C. J. Kickham  
D. L. Lionberger  
D. S. Luce  
F. P. McCarthy  
F. J. Moran

H. R. Morrison  
Hyman Morrison  
D. J. Mullane  
H. A. Novack  
J. J. O'Connell  
W. R. Ohler  
G. W. Papen  
H. A. Rice  
S. A. Robins  
D. D. Scannell  
J. A. Seth  
J. A. Sieracki  
S. L. Skvirsky  
E. C. Smith  
J. W. Spellman  
A. R. Stagg  
N. A. Welch  
P. R. Withington  
Marjorie Woodman  
E. T. Wyman

## NORFOLK SOUTH

F. A. Bartlett  
D. L. Belding  
Harry Braverman  
R. L. Cook  
Frederick Hinchliffe  
E. K. Jenkins  
N. R. Pillsbury  
R. G. Vinal

## PLYMOUTH

A. L. Duncombe  
P. H. Leavitt  
C. D. McCann  
R. C. McLeod  
G. A. Moore  
B. H. Peirce  
E. L. Perry

## SUFFOLK

H. L. Albright  
T. J. Anglem  
C. H. Bradford  
W. A. Browne  
A. M. Butler  
A. J. A. Campbell  
E. M. Chapman  
Henry Clifford  
A. P. Der Hagopian  
N. W. Faxon  
Reginald Fitz  
Maurice Fremont-Smith  
Channing Frothingham  
Joseph Garland  
G. L. Gately  
John Homans  
A. A. Horner  
L. M. Harzthal  
H. A. Kelly  
T. H. Landman  
C. C. Lund  
C. F. Maraldi  
F. W. Marlow Jr.  
Donald Munro  
F. R. Ober  
F. W. O'Brien  
J. P. O'Hare  
L. E. Parkins  
L. E. Phaneuf  
Helen S. Pittman  
J. H. Pratt  
J. H. Regan  
W. H. Robey  
Horatio Rogers  
H. F. Root  
C. M. Stearns  
Augustus Thorndike  
Conrad Wesselhoeft

## WORCESTER

A. W. Atwood  
George Ballantyne  
F. T. Bouquet  
F. B. Carr  
E. J. Crane  
G. R. Dunlop  
G. J. Elliott  
John Fallon  
H. L. Kirkendall  
D. K. McClusky  
J. M. Olson  
P. A. O'Toole

N. S. Scarcello  
J. J. Tegelberg  
G. C. Tully  
R. J. Ward  
B. C. Wheeler

## WORCESTER NORTH

J. J. Carley  
C. B. Gay  
J. C. Hales  
G. P. Keaveny  
J. V. McHugh  
C. S. McPeak

## APPENDIX NO. 2

## REPORT OF THE EXECUTIVE COMMITTEE

The Executive Committee of the Council met on September 3, 1947 in Sprague Hall, 8 Fenway Boston, Massachusetts at 4:00 p.m. Dr. Edward P. Bagg, president of the Society, presided. Present were Dr. Daniel B. Reardon, president elect, Dr. Charles J. Kickham, vice president, Dr. Elliot Hubbard, treasurer and representatives from all the district societies except Barnstable, Berkshire, Hampshire and Worcester.

The record of the meeting of April 23, as presented at the annual meeting of the Council on May 19, 1947 was submitted by the Secretary and was approved.

## COMMITTEE REPORTS

## Committee on Membership

The report of the meeting of August 13, 1947, as circulated in mimeographed form, was considered by sections and approved with one correction.

## Committee to Study Special Services

President Bagg, in commenting on the appointment of this committee, pointed out that the members representing the various associations were all approved by those associations so that whatever decisions were arrived at might be considered as authoritative.

The report, which had been distributed in mimeographed form with the Circular of Advance Information, was read by the Secretary and its acceptance is recommended by the Executive Committee.

Considerable discussion took place on the statement by Dr. Kemp Franklin on the failure of Blue Shield to determine accurately an applicant's yearly income, and the resolution offered by Dr. Scarcello, Worcester, that the Blue Shield through its employees determine accurately an applicant's yearly earnings before issuing the policy and secondly, that these earnings be reviewed each year.

The difficulties and the cost of determining these facts were brought out, and it was stated that the physician interviewing a patient can easily ascertain his income and so report to the Blue Shield.

The Executive Committee recommends that the Council refer this matter back to the subcommittee appointed to investigate the relations between members of the Massachusetts Medical Society and the Blue Cross and Blue Shield, for further study and conference with Dr. Charles G. Hayden, medical director of the Blue Shield.

That section of the report of the Committee on Public Relations containing the report of the Subcommittee on the Formation of a Woman's Auxiliary was discussed, and Dr. John F. Conlin, Suffolk, director of medical information and education, reported the establishment of the State Advisory Council and progress in Suffolk and Norfolk, two of the five districts that have approved district auxiliaries.

The acceptance of the report as a whole is recommended by the Executive Committee.

## Committee on Legislation

The Executive Committee recommends the acceptance of this report.

### *Committee on Arrangements*

The Committee on Arrangements reports that the next annual meeting of the Society will take place May 25 to 27, inclusive, at the Hotel Statler in Boston.

The Executive Committee recommends the acceptance of this informational report.

### *Committee on Finance*

The committee approved the recommendations made by the Treasurer, at the Council meeting on February 5, 1947, provisional on the raising of the annual assessment to \$25 00, that,

- 1 The refund to district societies be increased from \$4000 a year to \$8000
- 2 The total amount of the assets of the General Fund be set at \$250,000 and the balance of income over expenditures be automatically turned over to the Building Fund

The Executive Committee approves this report and recommends its adoption by the Council

### *Committee on Cancer*

The Committee on Cancer, in recommending approval of the request of the New England Deaconess Hospital for the establishment of a cancer-detection clinic, points out the opportunities that exist for funds for cancer research and cancer education, as shown in the committee's report.

The Executive Committee recommends that the question be referred to the Council without prejudice and that Dr Shields Warren, chairman of the committee, be asked to present the report and discuss it

### *Committee on Physical Medicine*

The Executive Committee recommends the acceptance of this report and the adoption of its recommendation

### *Committee to Meet with General Hawley*

This report contains the agreement, according to the Kansas Plan, entered into by the Massachusetts Medical Society and the Veterans Administration and signed by the President and Secretary in accordance with the vote of the Council on May 19, 1947

The Executive Committee recommends the acceptance of this report and the approval by the Council of a board of review to be nominated by the President according to Section 9 of the agreement.

The President at this point read a communication from the Council on Medical Service of the American Medical Association asking that representatives be sent to a conference on "Veterans Administration Home Town Medical Care Program" to be held at the Headquarters of the American Medical Association in Chicago on November 6, 1947

The Executive Committee recommends that the President be authorized to nominate such representatives

### *Committee to Study Malpractice Insurance in Massachusetts*

President Bagg, in presenting this report to the Executive Committee, called particular attention to its excellence and to the tremendous amount of work that had gone into its compilation

The Executive Committee recommends the acceptance of this report and the adoption of its first three recommendations. It further recommends that the fourth recommendation, asking for the discharge of the committee, be not adopted, but that the present committee, with proper replacements, be continued

### *Committee on New England Postgraduate Assembly*

The Executive Committee recommends the acceptance of this informational report

### *Committee to Establish a Pension Plan*

Dr Eliot Hubbard, in discussing this excellent report, pointed out that there is only one employee of the Society of long enough standing to be considered as a candidate for a policy under such a plan. Since the average salary of this employee over the years he has been with the Society has

been much less than his present salary, it seems fairer that a policy taken out for him should be based on his salary at the time the policy is dated

The Executive Committee recommends that this matter be referred back to the committee for further study

### *Advisory Committee on School Medical Services*

This report was the subject of considerable discussion in the Executive Committee, particularly regarding the recommendation that the present law requiring annual examination of school children be amended to provide for less frequent but more adequate examination. Discussion of this recommendation brought out the observation that no member of the committee had anything to do with school services and that it might be preferable to augment the committee or refer the matter to a group of school physicians for further consideration. Further discussion hinged about the controversial point as to whether school health should be under the department of education or that of health. This was not settled.

Debate over the desirability of the Society's drawing up a bill and arranging its introduction to the legislature was lengthy and varied. The Executive Committee finally agreed to recommend that it would be better for the Society to approve a bill introduced by some other agency, than to initiate one itself.

The Executive Committee hesitates to give an opinion on the thirteen recommendations of the Committee on Public Health that were referred to the Committee on School Medical Services. It does recommend the adoption by the Council of Recommendation 2, asking that a representative be sent to a conference on school health sponsored by the American Medical Association.

The remainder of the report is recommended for acceptance as one of progress, to be referred back to the committee for further study.

The Executive Committee recommends the acceptance of the excellent report of the Massachusetts representatives to the meeting of the House of Delegates of the American Medical Association at Atlantic City on June 9, 10, 11, 12, 1947

## OTHER BUSINESS

A letter was read from the Secretary requesting consideration of the matter of patients who wish to have physicians referred to them by the Secretary's office. The Executive Committee recommends that this problem be referred to the Committee on Public Relations.

A letter from Dr O'Hara was read stressing the urgency of making the Secretaryship a full-time position. The Executive Committee recommends that this matter and the relations between the Secretary, the Director of Medical Information and the Executive Secretary be referred to a committee of seven, to report at an early meeting of the Council for action.

A communication was read from Mr James A Morrison, manager of the Convention Bureau of the Boston Chamber of Commerce, addressed to Mr Boyd, the executive secretary.

This letter called attention to the new policy of the American Medical Association House of Delegates of having mid-year meetings away from Chicago. It was suggested that if the Massachusetts Medical Society cared to extend an invitation to the House of Delegates to hold its mid-year meeting and convention in Boston in the not too distant future, the Boston Chamber of Commerce would be glad to co-operate.

This matter was referred to the Secretary, to ascertain the opinions of the Massachusetts delegates and to act accordingly.

Dr John F Conlin, director of medical information and education, introduced the subject of the activities of the National Physicians Committee and the attitude that the Society should take toward them.

Dr Conlin gave the information that the National Physicians Committee is the third most powerful lobby in Washington, having expended about \$600,000 in the last year, mostly for lobbying. Although its objectives are approved by the House of Delegates of the American Medical Association, its methods have aroused considerable criticism. Na-

ional legislators and others are justly confused as to who represents the medical profession of the country.

The Executive Committee makes no recommendation for action by the Council.

A letter was read from Dr. George F. H. Bowers and other relatives of the late Dr. Walter P. Bowers expressing appreciation for the floral tribute sent to the funeral services.

The Secretary asked for instruction concerning the use of the Society's addressograph by district societies and others and was given authority to handle this matter with Mr. Boyd, as office business.

The meeting was adjourned at 6.30 p.m.

JOSEPH GARLAND, Secretary

## APPENDIX NO. 3

### REPORT OF COMMITTEE ON PUBLIC RELATIONS

At the last meeting of the Public Relations Committee, June 25, 1947, President Bagge expressed for the members of the Committee their sincere appreciation of the excellent work that Dr. Albert A. Hornor had performed as Secretary of the Committee on Public Relations. Dr. Harold R. Kurth, Essex North, was then elected as the new Secretary for this Committee.

President Bagge further reported that he had appointed as representatives to serve with Dr. Norman Welch on the Council of the New England state medical societies, Dr. Archibald J. Douglas, Hampden, and Dr. Gerald N. Hoeftel, Middlesex South.

Dr. Charles D. McCann, Plymouth, reported for the subcommittee that was appointed at the last meeting to investigate the relation between members of the Massachusetts Medical Society to the Blue Cross and Blue Shield as follows:

At the March meeting of the Public Relations Committee Dr. Harold R. Kurth, Essex North, offered a resolution in regard to the arrangement in the Blue Cross setup wherein the anesthetists are reimbursed only when they are on salary in a hospital.

The question then came up about professional and hospital service in general. After a good deal of discussion the undersigned committee was appointed by Dr. Dwight O'Hara to study any problem that might exist between members of the Massachusetts Medical Society and the Blue Cross and Blue Shield.

In order to obtain information in this respect the committee sent out a letter to the members of the Committee on Public Relations asking them to gather information concerning this problem and to bring that information to the next meeting of the committee.

On May 13, 1947, this subcommittee met at the Harvard Club with representatives of the Anesthesiological Society, the Roentgenological Society and the Pathological Society. Drs. Eversole and Wiggins, Drs. Sosman, Altman and Mueller, and Drs. Castleman and Nickerson represented the above-named societies.

These representatives were in accord that the setup in regard to professional and hospital service was very much mixed up, and it was their belief that services rendered by those groups should be taken care of under the Blue Shield program rather than by the Blue Cross.

At the annual Council meeting of the Massachusetts Medical Society Dr. Sosman offered a resolution to this effect, and it was voted by the Council that the President appoint a general committee from the Society to study the whole Blue Cross and Blue Shield plan.

In view of this decision this committee hopes that this report will be accepted and the committee discharged.

ALBERT A. HORNOR, M.D.  
HAROLD R. KURTH, M.D.  
CHARLES D. MCCANN, M.D.

As a result of the request by the subcommittee that the members of the Committee on Public Relations gather what information they could concerning this problem to be presented at this meeting of the committee, there ensued considerable discussion with reference to the relation of the members of the Blue Cross and Blue Shield.

Dr. Henry A. Robinson, Norfolk South, brought forth the criticism that in the lists of participating physicians of

the Blue Shield there was no way of distinguishing between regular physicians and osteopathic physicians. It was felt that this might lead to unnecessary confusion unless proper distinction be made. No action was taken by the Committee on Public Relations with reference to this criticism.

Dr. B. Appel, Essex South, stated that his district had requested him to present a resolution which was unanimously accepted by Essex South that medical service should not be considered under Blue Cross. He stated that the staff of the Lynn Hospital had also recorded itself as unanimously opposed to medical service being considered under Blue Cross. No action was taken by the Committee on Public Relations with reference to this resolution as it was felt that this matter at the present time was being discussed by the new Committee on Special Services.

Dr. H. M. Kemp, Franklin, stated that very little attempt was being made by Blue Shield to determine accurately an applicant's yearly income. This is necessary in determining whether an applicant is entitled to a limited or unlimited type of policy. At the present time the applicant's statement of income is accepted as correct. Attention was called to the fact that often a physician was entitled to make extra charges, fully aware that his patient's income was above the accepted \$3000, but found that he could not do so because the patient had been issued an unlimited policy, whereas in reality he should have been issued a limited policy thereby allowing the attending physician to make an extra charge. Such a situation often leads to some confusion in the patient-physician relation.

Dr. N. S. Scarcello, Worcester, offered the following resolution: That the Blue Shield through its employees determine accurately an applicant's yearly earnings before issuing the policy, and secondly, that these earnings be reviewed each year.

This resolution was adopted by the Committee on Public Relations.

There also followed some general discussion, more or less informative in nature, namely that Blue Shield allowed a larger fee schedule for obstetric care to the specialist than to the general practitioner doing the same type of work. It was the opinion of the Committee on Public Relations as a whole that at some future time there might be some more favorable revision of the fee schedule of the Blue Shield.

Following this presentation by the various members of the Committee on Public Relations, Dr. McCann moved for the acceptance of the report of this special subcommittee for the Blue Cross and Blue Shield problem. The report was accepted but the recommendation that this committee be discharged was rejected. It was believed that this subcommittee should continue to function to consider such additional information as may in the future be brought to its attention with reference to Blue Shield and Blue Cross problems and to report its findings to the Committee on Public Relations.

Dr. Milton Quinn, Middlesex East, reported for the Committee on the Formation of a Women's Auxiliary, stating that the Council had endorsed such a program for establishing such auxiliaries in the districts that so desired it. The Committee on Public Relations felt that the organization of these auxiliaries should be turned over to Dr. John F. Conlin, director of medical information and education.

Dr. Harold R. Kurth, Essex North, reported for the Committee, appointed by Dr. Dwight O'Hara to draw up resolutions expressing the sympathy of the Committee on Public Relations to the family of the late committee member, Dr. Daniel J. Ellison of Middlesex North. A letter to this effect was sent to his daughter, Mrs. Malcolm Stevens, Lowell, Massachusetts.

Dr. John F. Conlin stated that he would assume his new office as director of medical information and education on July 1, 1947. He urged the various members present to call upon him for whatever service he might give them in matters of public relations.

HAROLD R. KURTH, Secretary

## APPENDIX NO. 4

### REPORT OF THE COMMITTEE TO MEET WITH GENERAL HAWLEY

The committee, since reporting to the Council on May 19, has been successful in securing a contract with the Veterans

Administration providing for examination, treatment and counseling of eligible veterans in Massachusetts. The contract, which follows, was signed for the Massachusetts Medical Society by the President and Secretary on July 23, 1947, was received and approved by the Chief Medical Director of the Veterans Administration, General Paul R. Hawley, on the following day, and has been forwarded to the Director of Supply for appropriate action.

July 1, 1947

To the Administrator of Veterans Affairs

The Massachusetts Medical Society and the Veterans Administration for the purpose of establishing and maintaining a close working relation in order to establish a well-integrated service for providing medical care and treatment for veterans of the State of Massachusetts beyond those services available to the Veterans Administration in existing Veterans Administration facilities and installations, do hereby mutually agree as follows:

- (1) The Massachusetts Medical Society will request all its members to participate in a State-wide program whereby physicians in private practice in the State of Massachusetts will render medical services (examinations, treatments and counsel) in such cases as may be specifically authorized by the Veterans Administration.
- (2) The Massachusetts Medical Society will submit to the Veterans Administration a list of its members who desire to provide service for eligible veterans in the home communities of such veterans. This list may be augmented from time to time as additional physicians may indicate a desire to participate in the program. The physicians so listed will be fee basis physicians of the Veterans Administration. By notice in writing a physician may at any time request that his name be removed from the list of fee basis physicians.
- (3) The Massachusetts Medical Society will assist the Veterans Administration in establishing, for examinations and treatment, a list of competent specialists who meet the qualifications of specialist of the Veterans Administration.
- (4) Lists of physicians submitted by the Massachusetts Medical Society will be broken down by counties or districts in order that the veterans for whom services are authorized may select a physician practicing in his home community. The choice of the physician by the veteran, provided for herein, is not applicable to examinations for pension or compensation rating purposes. Such examinations may be performed only by a physician specifically designated for that purpose by the Veterans Administration.
- (5) Fees for medical services in authorized cases shall be paid by the Veterans Administration to the physician rendering the service in accordance with the Fee Schedule hereto attached, which is made a part of this agreement. The Massachusetts Medical Society warrants that the rates set forth herein are not in excess of the rate of fees charged other persons who are not Veterans Administration beneficiaries for the same or comparable services. It is mutually understood that the fees stated in the Fee Schedule represent the maximum amount that may be charged, and do not represent the amount to be paid in every case. The Veterans Administration will advise each physician of this provision, and will require each physician to certify in submitting his statement of account that the fees charged are not in excess of the fees charged by him for comparable service rendered non-veterans. It is understood that unusually involved cases and services not scheduled will be subject to review and recommendation by the Massachusetts Medical Society to the Veterans Administration for determination of the appropriate fee.
- (6) The Veterans Administration will handle administrative and clerical details in connection with the authorization of examinations or treatments and the maintenance of records, and will arrange for transportation of the veteran if necessary.

- (7) When authorizing treatment, the Veterans Administration will furnish to the veteran, proof of such authorization and a list of fee basis physicians in the county or district in which the veteran is located, in order that he may select his own physician for the services authorized.
- (8) The Veterans Administration will review reports of examinations and services to determine their adequacy. No fees will be paid by the Veterans Administration for reports that are not acceptable to the Veterans Administration or for services rendered in unauthorized cases.
- (9) The Massachusetts Medical Society will establish one or more boards of review composed of physicians. It shall be the duty of such board to review reports, which are deemed by the Veterans Administration to be inadequate or which do not meet the requirements of the Veterans Administration, to recommend, at its discretion, the disqualification of any physician for further work with the Veterans Administration whose work is found by the board to be incomplete or unsatisfactory, to advise and assist the Veterans Administration on other matters within the scope of this program.
- (10) It is agreed that services furnished under the agreement will be performed by licensed physicians. It is further agreed that physicians rendering services hereunder will be citizens of the United States who are doctors of medicine duly licensed to practice medicine and surgery in the State of Massachusetts.
- (11) This agreement shall be effective from July 1, 1947, to July 1, 1948, and may be terminated by either party by giving thirty (30) days' written notice to that effect.
- (12) This agreement, if mutually satisfactory, may be renewed indefinitely for a period of one (1) year each, upon notice in writing to the Veterans Administration at least sixty (60) days prior to the expiration of each period of one (1) year, and written statement from the Massachusetts Medical Society within thirty (30) days after such notification agreeing to the renewal.
- (13) No Member of or Delegate to Congress, or Resident Commissioner, shall be admitted to any share or part of this agreement or to any benefit that may arise therefrom unless it be made with a corporation for its general benefit.
- (14) The Massachusetts Medical Society agrees that in performing this agreement it will not discriminate against any employee or applicant for employment because of race, creed, color or national origin.
- (15) The Massachusetts Medical Society does not propose to make any charge for any service rendered to the Veterans Administration under this agreement.

For your further information, you are advised that it has been found necessary to adopt a policy that no physician will be permitted to accept fee-basis cases for the Veterans Administration in excess of \$6000 in any one year without the prior approval of this office. All Branch Medical Directors have been instructed to enforce this policy and to advise all participating physicians that it is in effect.

It will be further noted that in the paragraph which provides that physicians will be licensed, a provision has been added that they must be citizens of the United States. This is required by law. As you will see, no reference has been made in the proposed Agreement to the item "NOTICE TO BIDDERS," as this provision does not apply to an Agreement of this type.

It is also understood from the Chief, Out-Patient Division of the Boston Branch Office that Massachusetts Medical Society has agreed to accept the new Veterans Administration Fee Schedule (Form 10-2535a), which is attached hereto and made a part of this Agreement.

MASSACHUSETTS MEDICAL SOCIETY  
By EDWARD P. BAGG, *President*  
JOSEPH GARLAND, *Secretary*

The new Fee Schedule (Form 10-2535a) will be sent by the Veterans Administration to all participating physicians.

The Committee recommends that under Section (9) a Board of Physicians be appointed by the President or Council to review questionable reports or inadequate treatment.

ALLEN S. JOHNSON

JAMES H. BRAGGER

HUMPHREY L. MCCARTHY *Chairman*

## APPENDIX NO 5

### REPORT OF COMMITTEE TO SURVEY MALPRACTICE INSURANCE IN MASSACHUSETTS

In our report to the Council on February 5, 1947 it was stated that letters had been sent to

- I All fellows of the Massachusetts Medical Society together with a questionnaire.
- II Secretaries of all State Medical Societies in the United States.
- III Insurance companies underwriting most of the medical malpractice insurance in Massachusetts

#### I

##### SUMMARY OF REPLIES TO QUESTIONNAIRE

Questionnaires mailed	5,530
Questionnaires returned	3,701 (67%)
Resident fellows	3,446 (93%)
Nonresident fellows	255 (7%)
	3,701

##### A. Fellows with malpractice insurance

Resident fellows	2,717 (74%)
Nonresident fellows	145 (3%)
	2,862

##### Premiums paid

By 2,717 insured resident fellows	\$85,917 04	\$31 62
By 145 insured nonresident fellows	4,648 02	32 00
	\$90,565 06	\$31 64

Fellows paying less than \$50 00 90%  
 Fellows paying more than \$50 00 10%  
 Estimated total amount paid for premiums by total membership of 6,283 (as of January, 1947) \$153,074 32

(77% of 6,283 (4,838) × \$31 64 = \$153,074 32)  
 Estimated total amount paid for premiums by the 5,694 resident fellows (as of January, 1947) \$145,831 44

##### B. Fellows without malpractice insurance

Resident fellows (including 87 retired)	729 (19%)
Nonresident fellows	110 (4%)
	839

Estimated number of resident fellows without malpractice insurance 1,082  
 (19% of 5,694 = 1,082)

*Comment* Dr A. W. Allen chairman of the Committee on Medical Defense wrote "The annual cost of legal defense for the members not carrying insurance over a period of ten years would not be over \$1,000" and the attorney for the Massachusetts Medical Society wrote that during the ten years prior to January 1, 1947, the Committee on Medical Defense handled

Total number of cases	38
Cases actually tried	7
Judgment for defendant	7
Judgment for plaintiff	None
Cases settled	4

Cases disposed of without trial either by discontinuance or dismissal because of plaintiff's failure to prosecute 19  
 Cases pending 8

#### C. Type of practice of insured fellows

Medical	1,547 (42%)
Surgical	1,256 (34%)
X ray exclusively	59 (1%)
X ray plus other type practice	217

#### D. Companies doing most of the malpractice underwriting in Massachusetts

United States Fidelity and Guaranty Company	1,298 (35%)
Medical Protective Company	1,034 (28%)
Lumbermen's Mutual Casualty Company (including American Motorists)	170 (5%)
Hartford Accident and Indemnity Company	99 (3%)

There are approximately eighteen other companies each insuring less than 1%.

*Comment* Council on Medical Service, A. M. A., reported (J. A. M. A. May 10, 1947) that of 62 direct inquiries only 21 companies indicated they were writing malpractice coverage. 33 replied negatively, one stated that plans were underway and no replies were received from the other seven.

#### E. Suggestions volunteered

The Massachusetts Medical Society should have its own indemnity insurance 513 (14%)

The Massachusetts Medical Society should not have its own indemnity insurance 33 (9%)

Illustrative remarks in favor of Society having own insurance

- (1) "I would very much like not to buy commercial insurance if I were assured that I could be fully protected by the Massachusetts Medical Society"
- (2) "I have the impression our membership would be in a stronger position in case of individual suit if it was protected as a group — en masse — and by the Society rather than by many different companies all with different charges and varying degrees of responsibility"
- (3) "I believe the proposal of self insurance by the Massachusetts Medical Society is an excellent one."
- (4) "I am heartily in favor of a mutual co-operative malpractice insurance to be maintained and administered by the Massachusetts Medical Society. But — why not include health, accident, and retirement annuity?"
- (5) "I think the Society could handle this subject far better than the insurance companies."

#### Illustrative remarks against Society having own insurance

- (1) "I see no reason for a questionnaire of this sort, as I think the Society should stick to medicine and not to insurance."
- (2) "I do not believe we should in any way be in the insurance business. I know of a physician who cannot afford malpractice insurance. How long have we got to carry stungy, selfish, lazy, bottle fed members on our sturdy shoulders?"
- (3) "If any physician fails to carry malpractice insurance, then the Society should not defend him in case of a suit."
- (4) "State medical society insurance is poor business and probably not allowed by our charter. The defendant doctor is exposed to the personality and criticism of his colleagues, some of whom the defendant may not approve. Further the public may think the Society approved the defendant regard less of the action brought against him"
- (5) "Let's suck to our business and let the insurance companies suck to insurance"

#### Other remarks

- (1) "Returned to practice after three and a half years of service in the Army and have been unable to get coverage. I am a Middlesex graduate and I had coverage in the past but because I did not continue during my services in the Army I am not able to get coverage. I never had a claim against me in over twenty years of practice"



(2) "Was under the impression that the Society recommended and endorsed that all members be insured with United States Fidelity and Guaranty Company"

*Comment* This impression is probably due to the fact that the policy states, "Special Physicians' Liability Policy for members of the Massachusetts Medical Society"

II

REPLIES FROM SECRETARIES OF STATE MEDICAL SOCIETIES AND WASHINGTON, D C

Letters mailed	49
Replies	44
States not replying Vermont, Missouri, Maryland, Florida, Oregon	
A State societies with medical defense committee	28
Committees co-operating with both physician threatened and insurance company involved	24
Committees advising only the physician threatened	4
	28
B State societies defending members	18
State societies not defending members	26
C State societies paying indemnity	0
D Minimum rates charged by insurance companies in various states	
States not furnishing rates	17
States furnishing rates	27
	44

SOCIETIES WITH GROUP POLICY

State	Coverage	Rate
(1) Louisiana	\$ 5,000/\$15,000	\$15 00
(2) New Mexico	5,000/ 15,000	22 50
(3) New York	5,000/ 15,000	28 00
(4) District of Columbia	5,000/ 15,000	30 00
(5) New Hampshire	5,000/ 15,000	30 00
(6) Tennessee	5,000/ 15,000	30 00
(7) Washington State	5,000/ 15,000	30 00
(8) Delaware	10,000/ 20,000	25 00
(9) Connecticut	10,000/ 25,000	12 50
(10) Oklahoma	10,000/ 30,000	26 00
(11) Arkansas	15,000/ 30,000	28 00
(12) Alabama	(usual limits-?)	22 50

SOCIETIES WITHOUT GROUP POLICY

State	Coverage	Rate
(1) Ohio	\$ 2,500/\$ 7,500	\$17 00
(2) Massachusetts	2,500/ 7,500	17 00
(3) Kentucky	2,500/ 7,500	17 00
(4) Michigan	2,500/ 7,500	17 00
(5) Colorado	5,000/ 15,000	22 00
(6) Iowa	5,000/ 15,000	22 00
(7) Indiana	5,000/ 15,000	25 00
(8) Wisconsin	5,000/ 15,000	25 00
(9) Utah	5,000/ 15,000	35 00
(10) South Dakota	5,000/ 15,000	45 00
(11) California	5,000/ 15,000	60 00
(12) New Jersey	10,000/ 30,000	24 00
(13) West Virginia	10,000/ 30,000	25 00
(14) Nebraska	10,000/ 30,000	32 25
(15) Rhode Island	(usual limits-?)	20 00

*Comments* Of the 27 states furnishing rates

- a The highest rate is paid by California physicians who are individually insured, for \$5,000/\$15,000 coverage they pay \$60 00 annually
- b The lowest rate is enjoyed by Connecticut physicians who have a group policy, for \$10,000/\$25,000 coverage they pay \$12 50
- c In the seven states with group insurance, \$5,000/\$15,000 coverage, physicians pay from \$15 00 to \$30 00

d In the seven states with individual policies, \$5,000/\$15,000 coverage, physicians pay from \$22 00 to \$60 00

e In one state physicians with individual policies pay less than physicians in another state covered by group insurance In New Jersey physicians have individual policies and for \$10,000/\$30,000 coverage pay \$24 00 In Oklahoma under a group policy for the same coverage physicians pay \$26 00 but before the adoption of the group policy, individual physicians paid \$70 00

f In New Hampshire following the adoption of group policy about seven years ago there have been at least four successive reductions in rates For a surgeon with \$5,000/\$15,000 coverage the rate has been reduced from \$50 00 to \$35 00 The medical society also established a medical defense committee with which the insurance company co-operates and which serves in an advisory capacity to the physician against whom a claim has been made and to the insurance company Both the insurance company and the medical society believe that the establishment of the committee has been very helpful in decreasing the number of claims and the cost of premiums

E Liability insurance company organized by physicians  
In only one state have physicians organized their own mutual liability insurance company In 1944, physicians in the State of Washington organized the Washington Physician's Service Corporation This company is licensed to underwrite malpractice liability insurance if and when it is deemed necessary or desirable Its capital stock is \$150,000 00 and reserves are \$100,000 00 It is owned by the physicians of that State but is not, as yet, functioning The state medical society still has a group policy

*Comment* The Council of the Massachusetts Medical Society in 1921 discussed the advisability of developing a mutual insurance company for physicians in Massachusetts A plan was outlined whereby the members could form a company, pay in assessments, have the money deposited in a bank or invested in any way which an executive committee might see fit, and in that way provide for the administration of this type of business When the question was raised as to whether the state medical society could legally engage in this kind of business, Mr E P Saltonstall, at that time attorney for the Massachusetts Medical Society, stated

"Your articles of incorporation contain nothing which would seem to warrant your undertaking to pay verdicts or settlements in malpractice suits against its members and I should therefore assume that if you were going to undertake this work you would have to obtain an amendment to your charter"

That year (1921) the Massachusetts Medical Society recommended to its members that they take advantage of a group policy submitted by the United States Fidelity and Guaranty Company However, in 1923, the Attorney General (Jay K Benton) rendered an opinion that a group or blanket policy of liability insurance could not be issued to an association of dentists or physicians if the rates were discriminatory This opinion was written but not printed and has not been nullified The opinion was rendered because of complaints from the public that a cheaper rate was being given to physicians We were told by an assistant attorney general that there was nothing in the law to prevent medical societies from writing their own liability insurance Should the Massachusetts Medical Society undertake to do this, the assistant attorney general estimated that a surplus of about \$300,000 00 would be needed

III

REPLIES FROM INSURANCE COMPANIES

Most of the insurance companies to whom we wrote were co-operative. The Medical Protective Company, however, did not reply to either of our two letters

## A. Eligibility Requirements

- (1) One company stated it was a strict requirement of their company that every doctor they insure be a member of the American Medical Association or any of its state or county associations
- (2) One company stated that they did not accept all applicants. They may refuse to insure a graduate of an approved medical school and may accept a member who is a graduate of an unapproved medical school. However, they consider graduates of unapproved schools to be a much greater risk than those of approved schools. All applicants are investigated
- (3) Three companies stated that they accept graduates of unapproved medical schools, two stated that as a rule they did not. No company stated that they would not accept a graduate of an unapproved school

*Comment:* Some physicians, however, remarked on their questionnaires that they were unable to obtain malpractice insurance because they graduated from an unapproved medical school

## B. Co-operation with Committee of Society

All companies replying stated that they would co-operate with a committee of the Society. One company wrote, "We wholeheartedly welcome the opportunity of being able to co-operate with such a committee." The same company also stated that such a procedure would undoubtedly be an important factor in further reducing the cost of this protection to the members of the Society through the medium of favorable experience.

Another company suggested that if a member of a malpractice committee was in court and listened to every malpractice action in which adverse medical opinion evidence was to be given and made a complaint against any testimony that was untrue, that it would discourage such testimony. The company stated

"The mere knowledge that such a committee would sit in at all malpractice trials would deter and discourage all physicians from giving testimony of dishonest nature, and this deterrent effect would be even greater if the State Board of Registration did the same thing. The weak, incompetent, and the mentally dishonest would hesitate more than they do now to risk their license for a prospective expert fee.

## C. Rates in Massachusetts

- (1) United States Fidelity and Guaranty Company  
\$10,000/\$30,000 = \$19.00-\$70.00  
(depending on type of practice)
- (2) Hartford Accident and Indemnity Company  
\$10,000/\$30,000 = \$25.00-\$74.00  
(depending on type of practice)
- (3) American Motorists Insurance Company  
\$5,000/\$15,000 = \$25.00-\$40.00  
(depending on type of practice)
- (4) American Policyholders Insurance Company  
\$10,000/\$30,000 = \$20.00 (same rate for both practitioners and surgeons) and after 1st year less 15% dividend or \$17.00 a year
- (5) Medical Protective Company  
\$2,500/\$7,500 = \$17.00-\$23.00  
(rates obtained from printed literature)

*Comments:* (1) Since the survey of malpractice insurance in Massachusetts has been in progress two companies have reduced their premiums.

- (a) The United States Fidelity and Guaranty Company reduced their rates 5 per cent for all specialties except x ray

- (b) The Medical Protective Company reduced their premiums from \$2.00 to \$3.00 on a policy

\$2,500/\$7,500 limits (restricted) from \$19.00 to \$17.00  
\$2,500/\$7,500 limits (unrestricted) from \$25.00 to \$23.00  
\$5,000/\$15,000 limits (restricted) from \$22.00 to \$19.00  
\$5,000/\$15,000 limits (unrestricted) from \$30.00 to \$28.00

(2) Of the various companies investigated the American Policyholders Insurance Company, a subsidiary of the American Mutual Liability Insurance Company, offered the most attractive rates. Their policy is comparable to those of the other companies. Also,

- (a) They will insure all members of the Massachusetts Medical Society. They consider membership in the Society a sufficient recommendation.

(b) Their basic rate applies to all physicians — both general practitioners and specialists — only those giving x ray treatment and doing cosmetic plastic surgery have to pay a higher rate.

- (c) They will co-operate 100 per cent with a committee of the Society

(d) They will use the attorneys recommended by the Society

## IV

## ADDITIONAL DATA

*Incidence of Malpractice Suits*

Hubert Winston Smith of Boston in a series of articles entitled "Legal Responsibility for Medical Malpractice" which appeared in the *J A M A* during 1941 stated "Much is heard and said about the peril of malpractice claims but there is a definite lack of accurate information by which one might appraise the reality and size of this hazard." In an effort to obtain some factual data Smith collected and tabulated all the civil malpractice appeal cases decided by American courts from 1794 to January 1, 1940. In the following table is presented the appeal cases from 1930 to 1940.

## INCIDENCE OF APPEAL CASES OF CIVIL MALPRACTICE

*According to Population and Number of Physicians*

State or Jurisdiction	Total Cases (1930 to 1940)		Cases per Million Population (1930 to 1940)		Cases per Physician (1930 to 1940)	
	No.	Rating	No.	Rating	No.	Rating
Alabama	10	20	3 454	30	0 0046	16
Arizona	2	31	4 854	21	0 0038	22
Arkansas	3	37	1 464	42	0 0015	38
California	60	1	9 749	7	0 0055	12
Colorado	8	23	7 469	9	0 0041	19
Connecticut	12	15	6 892	11	0 0049	15
Delaware	1	46	3 601	28	0 0031	30
District of Columbia	7	27	11 164	6	0 0035	24
Florida	5	32	2 994	33	0 0025	32
Georgia	18	6	5 834	14	0 0065	9
Idaho	6	30	12 178	3	0 014	2
Illinois	15	12	1 904	39	0 0012	41
Indiana	7	27	2 014	38	0 0017	37
Iowa	8	23	3 134	32	0 0025	32
Kansas	5	32	2 682	35	0 0022	35
Kentucky	13	13	4 442	23	0 0046	16
Louisiana	9	22	4 221	24	0 0042	18
Maine	5	32	5 817	15	0 0052	13
Maryland	3	37	1 786	40	0 0010	43
Massachusetts	18	6	4 067	25	0 0024	34
Michigan	22	3	4 575	22	0 0037	23
Minnesota	17	10	6 428	12	0 0051	14
Mississippi	2	41	0 992	46	0 0013	39
Missouri	20	5	5 031	20	0 0032	28
Montana	3	37	5 565	16	0 0062	11
Nebraska	7	27	5 128	19	0 0039	20
Nevada	0	49	0 000	48	0 0000	48
New Hampshire	2	41	3 929	26	0 0033	26
New Jersey	11	17	2 536	36	0 0021	36
New Mexico	0	49	0 000	48	0 0000	48

State or Jurisdiction	Total Cases (1930 to 1940)		Cases per Million Population (1930 to 1940)		Cases per Physician (1930 to 1940)	
	No	Rating	No	Rating	No	Rating
New York	32	2	2 471	37	0 0013	39
North Carolina	18	6	5 172	18	0 0070	8
North Dakota	8	23	11 347	5	0 015	1
Ohio	11	17	1 619	41	0 0012	41
Oklahoma	16	11	6 301	13	0 0065	9
Oregon	12	15	11 741	4	0 0089	5
Pennsylvania	13	13	1 278	44	0 0010	43
Rhode Island	1	46	1 453	43	0 0010	43
South Carolina	1	46	0 537	47	0 0007	47
South Dakota	5	32	7 225	10	0 0088	6
Tennessee	10	20	3 473	29	0 0034	25
Texas	18	6	2 916	34	0 0026	31
Utah	8	23	15 414	1	0 014	2
Vermont	3	37	5 221	17	0 0039	20
Virginia	2	41	1 108	45	0 0010	43
Washington	21	4	12 665	2	0 010	4
West Virginia	6	30	3 217	31	0 0033	26
Wisconsin	11	17	3 759	27	0 0032	28
Wyoming	2	41	8 510	8	0 0076	7

**Comment** The cases decided by the appellate courts obviously represent only a fraction of the complaints of negligent practice. The appeal cases are those which usually involve a substantial "stake" — judgments ranging from \$1000 to \$50,000

Massachusetts with eighteen appeal cases between 1930 and 1940, was rated sixth, in other words, only five states had more such cases. On the other hand, in so far as cases per million population are concerned (4 067), Massachusetts was 25 and with 0 0024 cases per physician, Massachusetts was rated 34 — only fifteen states had less cases per physician

### CONCLUSIONS

- (1) More information on the subject of malpractice insurance should be accumulated
- (2) After sufficient data have been collected, the advisability of adopting a group-type of insurance should be considered.

### RECOMMENDATIONS

- (1) That the Massachusetts Medical Society should not undertake its own liability insurance at this time
- (2) That no one company be recommended exclusively at this time.
- (3) That a special committee of five fellows be appointed by the President to act in an advisory capacity to the Society and insurance companies in regard to malpractice insurance
- (4) That the present committee be discharged

CARL BEARSE, *Chairman*  
WILLIAM J BRICKLEY  
EDWIN D GARDNER  
DANIEL B REARDON  
GUY L RICHARDSON

## APPENDIX NO 6

### REPORT OF THE COMMITTEE TO ESTABLISH A PENSION PLAN

The problem before the committee was to arrive at some principles to be followed in establishing a pension plan for the employees of the Massachusetts Medical Society. Dr Robert N Nye, managing editor of the *New England Journal of Medicine*, was made a member of the committee in order to facilitate the adoption of any plan that might include employees of both the Massachusetts Medical Society and the *New England Journal of Medicine*

There are now nineteen employees, seven of whom work for the Massachusetts Medical Society and twelve who are employed by the *Journal*

The following points had to be considered

Who is to be included?

What amount is to be paid at retirement?

When shall the benefits be payable? (An employee will do only one of three things retire, die or resign. If the benefits accruing under these occurrences are determined, each activity of the employee is covered.)

Shall the employee contribute?

### Who Is To Be Included?

**Probationary period** It is essential that a probationary period be established before eligibility. Should this be one, two, three or five years? We recommend five years.

**Participating age** Little interest in a plan to benefit them at age sixty-five can be expected from young girls. Most of them do not expect to stay, and generally any money spent for them is wasted. What age for participation of employees shall be established? Should this be twenty-five, thirty or thirty-five? We recommend age thirty-five for women and thirty for men.

**Minimum years of service** It seems reasonable that if an employee is first employed by the Society late in life, the Society does not have an obligation to provide a pension for that employee. Another way to express this thought is: What is the minimum number of years of service that should determine whether an employee is entitled to a pension — should this be ten, fifteen, twenty or twenty-five years? We recommend twenty years.

### What Amount of Retirement Income Is To Be Paid?

Many plans give a pension credit for each year of service, generally 1 per cent or a fraction thereof for each year of service to date (past service) and 1 per cent for each year of future service. If the employee has many years of service, this provides a good pension, but this would not produce a pension commensurate with earnings for our top-salaried people. For example:

A female employee, age fifty-five, employed twenty-seven years, now earning \$4500 yearly, would be asked to retire on \$140 monthly, the equivalent of \$30 weekly, after thirty-seven years of service.

A female employee, age fifty-two, employed twenty years, now earning \$2500 yearly, would be asked to retire on about \$70 monthly, the equivalent of \$15 weekly, after thirty-five years of service.

A male employee, age fifty-five, employed ten years, now earning \$10,000 yearly, would be asked to retire on about \$170 monthly, the equivalent of less than \$40 weekly, after twenty years of service.

A male employee, age fifty-seven, employed twelve years, now earning \$4800 yearly, would be asked to retire on about \$88 monthly, the equivalent of less than \$20 weekly after twenty years of service.

We recommend that a pension of 50 per cent of the salary at the time the insurance is written be provided as a goal. If the recipient is granted increase in wages between the time he becomes eligible and the time he reaches the retirement age, proportionate increases in benefits would be added to the terms of the policy, but, in no case, irrespective of the wage at the time the policy is written, is the final monthly pension payment to be more than \$200.

### When Shall the Pension Benefits Be Paid?

**Retirement age** Shall retirement be at fifty-five, sixty or sixty-five? The longer the period of funding, the smaller annual amount is required, also, the amount needed to buy a pension for an employee age sixty-five is less than for a pension at age sixty. Our recommendation is age sixty-five.

**Death** Certainly the Society does not want to profit by the death of an employee, accordingly we recommend that whatever death benefit is available under the annuity contract be paid over to the beneficiary of the employee.

**Disability or early retirement.** If the employee withdraws within five years of membership (ten years of service), he receives no part of the annuity if he leaves after five years of membership, he is entitled to 25 per cent of the annuity already purchased, the balance goes to the Society. The amount he receives increases thereafter. He may receive this either in the form of cash (the proper percentage of the cash value of the annuity) or in the form of an annuity (that percentage purchased at the time of disability or early retirement) to be paid by the insurance company when he reaches retirement age (sixty five).

#### Shall the Employee Contribute?

This is a matter of personal opinion. The persons to be covered under our recommendations would appear to be able to make some contribution, but it is our recommendation that such an amount as they may elect to contribute should be used for the purchase of increased annuity rather than to decrease the amount paid by the Society for the basic annuity.

#### Summary of Recommendations

**Eligibility.** Those employees age thirty if male and thirty five if female, who have been in our employ five years or more and who at retirement will have had twenty years service.

**Retirement pension.** Fifty per cent salary at the time the insurance is written.

**Death benefits.** Full amount, as provided by the insurance company.

**Termination-of-service benefits.** Prior to first five years, one fifth to nine years, 25 per cent; ten to fourteen years, 50 per cent; fifteen years or more, 100 per cent.

With the above recommendations in mind it is found on looking over the seven employees of the Massachusetts Medical Society that only one—a man aged fifty-seven years—is eligible. The others are either under participation age or have not been in our employ for a sufficient period of time. This being the case the simplest solution would seem to be to make no attempt to establish a program of group insurance and retirement.

Your committee recommends that an individual contract be made for this employee in the cost of which he may participate to whatever extent he wishes and that the selection of the company be made on the basis of both his wishes and those of the Treasurer of the Society. We have data from several companies concerning the cost of this type of retirement plan. It is suggested that this method might well be followed in each individual case as the person becomes eligible for insurance and a pension. It is further suggested that the individual arrangement be made by the Treasurer of the Society.

As an illustration of the probable cost of a typical retirement policy the annual rates of four companies on the basis of \$100 of pension are as follows:

Age 35	\$ 411 20 to	500 60
Age 45	679 10 to	817 00
Age 55	1 488 00 to	1 746 40

In view of the above data the committee recommends that no fund be established at the present time for the purpose of providing insurance and pensions for employees, but that individual arrangements be made as the occasion arises.

ROBERT W. BUCK, CHAIRMAN  
ELIOT HURNARD, JR.  
ROBERT N. NYE  
GEORGE W. PAPPEN

Society and health and education officials on both state and local levels" submits the following informational report together with certain recommendations.

For the information of the Council —

(1) On May 28, 1947, your committee met with Mr. Arthur Pierce, superintendent of schools of Wellesley, appointed by the Massachusetts School Superintendents' Association to be the liaison person between the Superintendents' organization and your committee.

(2) Your committee submits for your information the copy of a letter being sent to all district society secretaries requesting the submission of physicians' names to be appointed to the district committees on school medical services.

(3) The Council referred to this committee the following recommendation of the Committee on Public Health: "That the Massachusetts Medical Society approve suggested legislation providing for full time qualified medical health officers whenever possible and that school medical service be under their direction. The remuneration for full time medical health officers should be sufficient to attract qualified personnel." A consideration of this recommendation led to so much discussion that it was decided to table this for the present, to allow for further information and discussion.

(4) The Council referred the following recommendation to the committee: "Examination by a private physician be acceptable to the school medical authorities if the examination is recorded on the school health form." Your committee changed this to read, "Examination by a licensed private physician be acceptable to the school medical authorities if the examination is recorded on the school health record form." This point was referred to the Commissioner of Public Health and Dr. Getting replied that he did not think this should be made the subject of a formal opinion by the Attorney General's Office on this point of law. It was Dr. Getting's opinion to which the Assistant Attorney General Roger Clapp concurred that "it would be entirely within the province of a school department to accept a medical examination by a licensed physician."

(5) The Council referred the following recommendation to the attention of this committee — "That teacher training be provided in teachers' colleges in growth and development of children in teacher observation of the health of children and in health education." This recommendation led to a great deal of discussion and the matter was tabled with the suggestion that a subcommittee of this committee and educators be appointed to make a further study and submit recommendations concerning teacher training in the field of health.

(6) The Council referred the following recommendation to this committee — "The State Dental Society be encouraged to participate in the school health program to a greater extent." Your committee changed this to read, "The committee would pursue the co-operation between the medical and dental societies in the school health program."

Your committee accepts the following three recommendations unchanged.

(7) "That qualified district and community nutritionists provide for nutrition phases of local school health programs including school lunch programs."

(8) "That there be provided adequate physical, mental and psychological examinations of entering school children early enough so that there may be correction of remediable defects and completion of immunizations before the child enters school."

(9) "That the presence of parents be urged at the examination of younger children so that parental understanding of health needs may be insured."

(10) Your committee changed the following recommendation — "That the interpretation be provided by the school physician and nurse of health findings to older children so that they may be motivated to do what is in their power to improve their health" to read "The interpretation to be provided by the school physician and the nurse, acting under his supervision of health findings to older children so that they might be motivated to do what is in their power to improve their health."

(11) Your committee changed the following recommendation — "That there be provided interpretation by the school physician and nurse of health findings to teachers so that they may understand the health status of children under their daily observation" to read "That there be provided interpretation by the school physician and the nurse, acting under his supervision of health findings to teachers so that they may assist the school nurse in emphasizing conditions to

#### APPENDIX NO 7

#### REPORT OF THE ADVISORY COMMITTEE ON SCHOOL MEDICAL SERVICES

The Committee on School Medical Services appointed by the Council on February 5, 1947 to "establish an effective liaison between representatives of the Massachusetts Medical

parents" to read "To be provided by the school physician and the nurse under the guidance of the school physician, the interpretation of health findings to teachers so that they may understand the health status of children under their daily observation, may make suitable provisions in classrooms and may assist the school nurse in emphasizing conditions to parents."

(12) Your committee changed the following recommendation — "That there be co-operation with the physical education program" to read, "The physical education program is an integral part of the over-all health program and should be worked out co-operatively with the school health authorities."

(13) Your committee changed the following recommendation — "That continuing staff education for health personnel be provided under suitable auspices" to read, "continuing staff education for public health personnel should be encouraged."

#### RECOMMENDATIONS

(1) Your committee recommends that the present law requiring annual examinations be amended to provide for less frequent, but more adequate examinations on a spaced and selective system at least four times during the child's normal school life.

(Your committee suggests that the Executive Committee arrange with the Legislative Committee and Dr. Conlin and others authorized to draw up such a bill and present it to the Council at its October meeting. Mr. Pierce offered to secure approval of the Massachusetts Superintendents' Association through Mr. Burr Merriam and of the Massachusetts Teachers Federation through Mr. Hugh Nixon. He suggested that the Massachusetts Women's League and the League of Women Voters be asked to support the bill.)

(The opinion of the Commissioner of Public Health was sought to see if an "adequate" examination included the disrobing of children. Dr. Gettling's opinion in which the Assistant Attorney General, Roger Clapp, concurred was "that the disrobing of children is necessary if an adequate physical examination is to be made.")

(2) The American Medical Association is sponsoring a conference on the Co-operation of the Physician in the School Health and Physical Education Program, October 16-18, 1947, under the auspices of its Bureau on Health Education. The conference will be held at the Hotel Moraine, Highland Park, Illinois. Invitations to send representatives will be extended to state medical societies (one representative from each state), state departments of education, health, teacher education and education administration (one from each state).

Dr. O'Hara referred the invitation to the Committee on School Medical Services with the notation that in his opinion the Massachusetts Medical Society should be represented and that this committee should ask for an extraordinary appropriation at the October meeting to cover the expenses of such representation.

Your committee considered the invitation and agreed that the Massachusetts Medical Society should be represented by a member of the Committee on School Medical Services and that either the chairman or Dr. Morris might be able to attend.

Your committee, therefore, recommends that the Council approve such representation and grant an extraordinary appropriation to cover the expenses of the trip.

STEWART H. CLIFFORD, *Chairman*  
ELMER S. BAGNALL  
JOSEPH GARLAND  
FLORENCE MCKAY  
ERNEST MORRIS  
THOMAS F. REILLY  
JAMES O. WAILS

#### APPENDIX NO 8

REPORT OF THE MASSACHUSETTS REPRESENTATIVES TO THE HOUSE OF DELEGATES OF THE AMERICAN MEDICAL ASSOCIATION, ATLANTIC CITY, JUNE 9, 10, 11 AND 12, 1947

The meeting of the House of Delegates opened promptly at 10 a m., June 9, 1947. Out of a total of 175 delegates avail-

able, 173 delegates indicated their presence — an excellent showing. Five of your delegates were present: David D. Scannell, Leland S. McKittrick, Charles J. Kickham, Allen G. Rice (alternate for Charles E. Mongan) and John I. B. Vail (alternate for Walter G. Phippen). The first business of the meeting was the balloting for the recipient of the Distinguished Service Award. Two surviving out of three names were those of Dr. Henry A. Christian and Dr. Isaac A. Abt of Chicago. The Christian vote was 100, Abt's, 73. Although notified at once of his selection, Dr. Christian was unable to be present the following evening to receive the award in person.

There followed the usual addresses of the Speaker, the President and the President-Elect. All these addresses were of a very high quality and deserve to be read as they appear in the *Journal of the American Medical Association*, June 21 and later. We wish to call attention to the addresses of President Bortz on the morning of the first day and on the evening of the second day when he was inducted into office. They were unusually thoughtful and timely.

Following this, came the reports of the officers, many of them by title, since the delegates had read them in the handbooks issued several weeks before the meeting. Excellent addresses followed by Major-General Raymond D. Bliss, Surgeon-General of the United States Army (successor to General Kirk) and Rear-Admiral Clifford A. Swanson (successor to Admiral Ross McIntyre).

Assignments were then made to the various committees, which on this occasion concerned our group very little. We wish here to repeat what we have stated on many previous occasions: membership on these reference committees is the hardest kind of work — under pressure and under debate. This time it was harder than ever because of the multiplicity of measures introduced, requiring an unusual amount of deliberation. One thing that slowed up the meeting of the House was the introduction of foreign visitors and the reading of congratulatory messages from all over the world. There were present more than fifty visitors from foreign countries and at least twenty-five or thirty were presented during the first two days, some merely taking a bow, but many choosing to pay verbal compliments on the centennial of the Association. One speaker appearing on this first day was Admiral Boone whom we heard in San Francisco in July, 1946, on the same subject, viz., "Health Conditions in the Soft Coal Industry." He is an admirable speaker, clear-headed, convincing and brief. This time, as last, he made a very strong impression. The Government is most fortunate in having such a man in its service. His address should be read (Page 714 in the *Journal of the American Medical Association*, June 21).

One of the most important reference committee reports was submitted on the second day. This came from the year-old Interim Committee on Executive Session, appointed in San Francisco in 1946, this committee had rendered its first report on the Rich Associates in Chicago in 1946 and had been continued for further study. The Committee consisted of Bates of Pennsylvania, Buntz of Georgia, Carey of Texas, Hein of Ohio, Lewis of New Jersey, McGlendon of California, and Scannell of Massachusetts. The matters at issue were public relations and the association of the American Medical Association with the National Physicians Association. The Reference Committee, after long study and considerable expense, brought in a report completely justifying the liaison or co-operation with the National Physicians Association, concluding by recommending that a change be made in the public relations consultant of the American Medical Association. As a matter of fact, the Rich Associates through Mr. Rich himself and the newly appointed Executive to the General Manager, Mr. Swart, anticipating our report, resigned even before our report was made to the House of Delegates. Our report was unanimously approved and the committee discharged.

At the dinner meeting given that evening to the House of Delegates by the Trustees, there was presented by a member of the Postmaster-General's Department the new stamp commemorating the Centennial of the American Medical Association. This is an unusual stamp and of particular significance. The ninety million stamps issued to the Atlantic City visitors were, I believe, all sold on the fifth day of the convention (many visitors taking sheets of 500-1000 of these beautiful

three-cent stamps) They portray the doctor at the bedside of the sick child with the peasant parents near by.

All through the meeting, in the reports of officers, reference committees, and other addresses, emphasis was placed on the general practitioner his important place in the community and the necessity for helping him in all ways, especially with scientific exhibits. This came to a climax when on the last day of the meeting of the House of Delegates it was decided to hold the supplementary or mid winter meeting of the House in different centers each year (instead of in Chicago as heretofore) followed by a two-day scientific exhibit for the general practitioner only. This gives the answer to those who have insisted that the day of the general practitioner is done. This is an epochal event and one of the most important moves the American Medical Association has ever made.

There is much profitable reading in the pages of the *Journal* with reference to this centennial meeting; this is to be found in the issues of June 21, 28 and July 1. Especially worth while are the reports of the councils on Medical Education and Hospitals, National Emergency Medical Service, Medical Service and so forth.

On the second morning short addresses were made by various visiting guests particularly those from England, Iceland, Australia, Denmark, Syria, Cuba, Venezuela, Guatemala, Canada, Switzerland, Mexico, Colombia, China, Argentina, Norway, Hungary, Saudi Arabia, Panama, Belgium, Sweden and Finland. Various resolutions having to do with the specialty boards and their policies were introduced and freely discussed. Most important was the supplementary report of the Council on Medical Education and Hospitals, which we believe should be presented in full. The report is as follows:

MR. SPEAKER. The Council on Medical Education and Hospitals has directed me to introduce the following supplementary report:

Considerable thought has been given to devise ways of upholding the prestige of general practitioners so that they may be encouraged to provide the citizens of our country with the kind of medical care which they are peculiarly qualified to furnish and for which there promises to be continued need.

The establishment of a Section on the General Practice of Medicine by this House in 1945 was an important step forward. Interest in this section was at once apparent as shown by a registration of 939 at the 1946 Scientific Assembly and by the attendance of these registrants at the various meetings. This House has also expressed its approval of the organization of sections on general practice in state and county medical societies.

In spite of this, certain hospitals have inaugurated as a matter of policy limitation of their staff appointments to physicians certified by specialty boards or holding membership in certain medical societies. Such a policy is contrary to the principles of the Council and seems unsound. In publications which have dealt with hospital standards the Council has expressed repeatedly the need for a hospital staff of high quality; it has never mentioned certification by a specialty board or membership in a special medical society as an important credential.

Certain institutions have assured for themselves the inclusion on their staffs of properly qualified general practitioners by the intramural establishment of "General Practice Sections". An excellent description of how such a section actually operated over a period of eight years in a 450 bed hospital appeared on pages 15 through 16 of the May 3, 1947, issue of the *Journal of the American Medical Association*. Reprints of this article will be distributed by the Council to every registered hospital in the United States.

On the whole, so much uncertainty appeared to exist in the minds of many boards of trustees of hospitals about the propriety of establishing such sections as to lead this House at its meeting in San Francisco a year ago to adopt a significant resolution. This was reported favorably by the Reference Committee on Medical Education and adopted by the House. part of this resolution is quoted

"WHEREAS Many hospitals have not established general practice sections in their visiting active staffs and their governing heads are doubtful whether such action has the

approval of the bodies which set up the rules and regulations for the approval of their hospitals for interns and residents, therefore be it

Resolved, That hospitals should be encouraged to establish general practitioner services. Appointments to a general practice section shall be made by the hospital authorities on the merits and training of the physician. Such a general practice section shall not prevent approval of a hospital for training of interns and for residencies. The criterion of whether a physician may be a member of a hospital staff should not be dependent on certification by the various specialty boards or membership in special societies.

Copies of this resolution have been sent to the American College of Surgeons, the American College of Physicians, the American Hospital Association, the Protestant Hospital Association, the Catholic Hospital Association and to each hospital registered by the Council.

To carry forward the intent of the resolution the following report was published by the Council in *The Journal*, page 95 in the May 3, 1947 issue.

At the direction of the House of Delegates of the American Medical Association some years ago, the Council on Medical Education and Hospitals formulated standards for the establishment of American boards for the certification of specialists and for the conduct of hospital residencies providing training in the various special fields of medicine. The aim was to improve the quality of training at this level of medical education. The physician responsible for directing such hospital training should himself have had training and experience approximately equivalent to that required of certification applicants whether or not he is actually certified. But it was never intended that staff appointments in hospitals generally or even in hospitals approved for residencies should be limited to board certified physicians, as is now the policy in some hospitals. Such policies if practiced extensively are detrimental to the health of the people and therefore, to American medicine. Hospital staff appointments should depend on the qualifications of physicians to render proper care to hospitalized patients as judged by the professional staff of the hospital, and not on certification or special society memberships.

In this opinion the Council has the full concurrence of the Advisory Board for Medical Specialties which represents all the American Boards in the specialties. At the February 1947 meetings of the Advisory Board it was unanimously voted to adopt as the sentiment and policy of the Advisory Board the recent resolution passed by the American Board of Surgery which reads:

The American Board of Surgery is not concerned with measures that might gain special privileges or recognition for its certificatees in the practice of surgery. It is neither the intent nor has it been the purpose of the Board of Surgery to define requirements for membership on the staffs of hospitals. The prime object of the Board is to pass judgment on the education and training of broadly competent and responsible surgeons—not who shall or shall not perform surgical operations. The Board specifically disclaims interest in or recognition of differential emoluments that may be based on certification.

Since February several separate American Boards in the various specialties have taken similar action. The Council on Medical Education and Hospitals of the American Medical Association is completely in accord with this principle.

The Council now asks authority to use still another level to carry forward the intent of the resolution. It recommends that Section 3 paragraph 6 of the "Essentials of a Registered Hospital" now reading

'6. Staff sections, such as medicine, obstetrics and surgery should be organized as may seem wise  
be amended to read

6. Staff sections such as medicine, obstetrics, surgery, general practice etc., should be organized as may seem wise

This amendment is proposed in the belief that even so small a change in words of the Essentials may be of help in promoting the intent of the resolution adopted by this House a year ago.

The desirability of doing this is plain. The establishment of an American Board of General Practice is being discussed by the Section on the General Practice of Medicine, by the Council and by the Advisory Board for Medical Specialties. The wisdom of establishing such a specialty board at this particular time is debatable. Wider realization and greater use of the contributions which skillful general practitioners can bring to hospitals may make superfluous the need for their certification by a specialty board.

Also discussed at length in the report of the Board of Trustees was the formation of a World Medical Association. At a preliminary meeting held some weeks ago, Drs. Bauer and Henderson representing the American Medical Association went to London, and they, with Dr. Irons, are to represent the Association at a meeting to be held a little later this year in London. This would seem to be the opportunity and responsibility of the American Medical Association to assist in the development of a world medical front in meeting problems as they develop in the councils of world health organizations and in the divisions of the United Nations.

Simultaneously, there is groundwork being done for a Pan-American Medical Federation. Here, also, much work has been done by three members of the American Medical Association in connection with members from Canada and Central and South America. A fairly long plea for this Pan-American Federation was presented by the delegate of the Pan-American Congress from Cuba, his proposals can be found on Page 796 of *The Journal*, June 28.

At the inter-session luncheon of the House of Delegates Tuesday, June 10, excellent addresses were made by Secretary of War, Robert P. Patterson and Assistant Secretary of Navy for Air, John N. Brown. Secretary Patterson's speech was so important that we believe it should be incorporated in this report and later printed as a separate article in the *New England Journal of Medicine*. Some of the measures he proposes chart a new policy in a governmental agency to provide medical care in peacetime. The reading of this report is a "must" and is as follows:

Your consideration in inviting me here this afternoon to discuss the Army Medical Corps' pressing problem is a courtesy that I appreciate very much.

You are a busy group, with many important questions to discuss, so I shall get right down to the facts. However, I do want to take time to repeat the statement that I made this morning before the General Scientific Meeting.

"The medical service of the American Army in World War II was the finest of any Army in the world."

It is one thing to express a determination on the Army's part to maintain its medical service on a par with that provided from 1941 to 1946. It is quite another thing to recruit in peacetime the number and type of physicians that a medical service of this high quality requires.

The motive of patriotic self-sacrifice that led forty-seven thousand of the medical profession to volunteer their services in war cannot be depended on today to provide the necessary physicians for the Army. It is not to be expected that it should. The fact remains, however, that the Army must continue to count on the patriotism of the medical profession in other ways than direct service. Your continued interest in the Medical Department, your co-operation and your support are necessary. Without them no program can be successful.

I need not labor the point that in these troubled times the Army is indispensable to our national safety. Most of our soldiers are on active service overseas, chiefly in Germany, Austria, Japan and Korea. They are keeping the peace, with the result that we may meet here without excursions and alarms. But the Army cannot be strong unless we have a strong medical service. The predicament of the War Department in getting medical

officers is therefore a matter of patriotic concern to the whole medical profession. If there is a matter of greater urgency, I do not know what it is.

Present plans of the War Department call for an Army of 1,070,000 men. We shall need an Army of more or less that size so long as we have our present commitments for occupation abroad and national security at home.

Six thousand doctors are required to provide adequate medical service for an army of 1,070,000 strength. At present we have five thousand doctors in the Medical Corps. However, only eleven hundred of these are in the Regular Army. If the present state of national emergency were to be terminated we would lose all our doctors except those in the Regular Army. Even if the emergency remains in effect, the younger officers now on temporary service will be leaving in large numbers on expiration of their two years' service. Unless prompt measures are taken, the prospects are that we will be short thirty-seven hundred doctors by mid-year of 1949, and short forty-four hundred doctors, or more than two thirds of our requirement, by mid-year 1950.

We must therefore make every effort to induce as many as possible of these officers to volunteer for further duty in the Medical Corps, and we must also actively recruit physicians from civilian life.

To date the results of our efforts to build up our professional medical personnel have been disappointing. The response to the invitation to medical officers on temporary duty to become part of the Regular Army fell far below expectations.

There are many reasons why medical officers of the Army of the United States — the A U S — did not respond to the invitation to become part of the Regular Army. I do not propose to go into those reasons. We know them, and you know them. Through the work of the Secretary of War's Medical Advisory Committee that I asked to help the War Department on its medical program, those reasons were compiled and presented to the Army in a way that required the Army to do something by way of cure.

The Army is going to do something about it. We have already begun — and we intend to continue, with your help, until we have solved the problem. A major step in our program to provide a professionally competent and adequate medical service for the Army is the introduction in Congress of legislation to "provide for the procurement of physicians and surgeons in the Medical Department of the Army." That legislation is identified in the House of Representatives as H. R. 3174, and in the Senate as S. 1143.

At a casual reading of the bill, it would seem that the principal purpose of that legislation is to provide more pay for medical officers. Such a conclusion would confuse the means with the end. The actual purpose of that bill is to promote and enhance the professional standing of the Army Medical Corps.

The War Department is convinced, after more than one hundred and seventy years of close association with the medical profession, that the skill of the American medical man cannot be bought for dollars and cents. But it is given generously as a matter of patriotism and professional pride. The doctor can have such a pride in the Army medical service only when that service has the highest possible professional dignity. I am already on record with the statement made last year that it is my sincere desire to maintain the medical standards of the Army at the highest possible professional level. I want now to reiterate that statement as expressing both the Army's and my determination. General Eisenhower also expressed the Army's position when, in a memorandum to the Army's top commanders, he said:

The realization of our objective places upon us, the military, the challenge to make our professional officers the equal in knowledge and training of civilians in similar fields and make our professional environment as inviting as those outside.

The War Department knows that a medical service equal to the needs of our modern Army can be obtained and continued only by establishing a professional level

equal to the best in civilian practice. Establishment of that professional level is our goal. All other advances benefits or gains serve only as steps toward that goal.

Yet, we intend to be practical in seeking our objective. We realize that no governmental agency can hope to give to the doctors who will serve it a direct financial return equal to what the best men in the profession can make in civilian life. At the same time, we cannot expect and do not intend to ask competent doctors to devote their years to the Army without compensation that at least is worthy of the important position they hold and adequate for their needs.

The legislation now before Congress is our answer to that part of the problem and for that reason I want to go over it with you. It must have your support, not only to win Congressional approval, but to serve its purpose—the improvement of the professional status of the medical officer.

The first part of the bill would give to all Medical Corps officers with less than thirty years service \$100 a month extra pay. The increase would apply both to regular officers and to nonregular officers who volunteer for extended active duty for a period of one year or longer.

The next three sections of the bill are the basis of our efforts to improve the professional status of the Medical Corps. Two of these sections also deal with specialists, and they are of great importance. The quality of medical care will be determined by fulfillment of our needs for surgical and medical specialists. These we must have if we are to provide the Army with a high standard of professional care.

About thirty per cent, or eighteen hundred, of the six thousand medical officers required for the Army of the present strength should be specialists. So far, we have about one fifth of that total, including those in retraining. In obtaining sufficient specialists, the Army is handicapped not only by the small pay in comparison with earnings in civilian practice, but also by the competition of other Government agencies paying more than the Army presently is authorized to pay.

Titles II and IV of the bill now in Congress would do much to improve the Army's position in retaining and obtaining specialists for the Medical Corps.

Title II provides for an increase of 25 per cent in the base and longevity pay of those Medical Corps officers who qualify as specialists, during the time such officers are so qualified. Certification of a recognized American as a Specialty Board would be required for qualification as a specialist in the Medical Corps but all Medical Corps officers, regular and non regular alike, would be eligible to qualify. The Veterans Administration already has the right to make such extra payments to its specialists.

Title IV of the proposed legislation would permit the Army to make original appointments of outstanding medical specialists in the Medical Corps from civilian life, in grades and ages above those in which such appointments now can be made. Under the bill appointments as specialists could be made in any grade up to and including colonel, the grade for each appointee being determined by his qualifications. Doctors thus commissioned from civilian life would be only those certified as specialists by a recognized American Specialty Board. In the past statutory limitations prevented our commissioning such officers at grades commensurate with their abilities. As a result, we were unable to obtain the services of specialists even though they were available.

If the Medical Corps is to attract physicians through the opportunities it offers for professional work of high quality it is obvious that within the Corps there must be men in key positions who set the standards for professional work and guide the careers of young medical officers. To provide such advisers to the Surgeon General, the Bill, under the provisions of Title III authorizes the direct appointment in the grade of brigadier or major general of four physicians distinguished respectively in the fields of medicine surgery neuropsychiatry and preventive medicine. The mission of these leaders would be to supervise professional standards, educational programs and the assignments of professionally qualified

officers. They will carry in addition to their rank, the titles of professors.

Appointments to the four professorships would be made by the President of the United States, with the consent of the Senate.

The Army Medical Department hopes to meet its responsibilities with commissioned personnel. However if we are unable to procure the necessary military personnel we must be able to utilize the services of civilian doctors. Title V of the new bill will give us the necessary authority. It will permit the appointment of civilian physicians, in such numbers and for such periods of time as may be necessary, without regard to Civil Service requirements, and is substantially identical with the authorization given some eighteen months ago to the Veterans Administration.

Properly qualified civilian doctors would be appointed under this legislation in one of six grades, the annual pay scale of which would range from \$3640-\$4300 for junior grade up to \$8750-\$9800 for chief grade. Further, if a civilian doctor thus appointed is designated a specialist, he would receive an allowance equal to 25 per cent of his base pay up to a total of \$11,000 a year.

Employment of civilian physicians on a temporary full time, part time or fee basis also would be authorized by this legislation.

These five sections sum up the legislation now before Congress to improve the professional status of the Army Medical Corps. They are in the opinion of the War Department the best answer to the problem of procuring qualified medical officers.

Other plans were considered and found wanting. These included subsidization of the education of prospective Medical Corps Officers and establishment of an Army medical school. Still other recommendations and suggestions for improving the Army medical service are being studied seriously.

The basic need of an adequate Army medical service is a professional competence second to none. The legislation now before Congress is designed to go a long way toward making that high grade professional attainment possible. The War Department will do everything else in its power to establish and foster the professional environment required. I ask your support of this legislation and of our entire Medical Corps program.

The meeting lasted four full days mornings and after noons. As a result, very few members of the House of Delegates had an opportunity to visit the scientific exhibit by all odds the best ever presented. Likewise, the commercial exhibit was a remarkable piece of organization. Obviously the opportunity for listening to valuable papers on clinical and basic scientific subjects did not exist for the delegates. In short the four-day session for the House of Delegates was uninterrupted work. On the final afternoon (Thursday) the following were the highlights

1. The election of Dr. Sensemich as president-elect.
  2. The election to the Board of Trustees of Dr. E. J. McCormick of Toledo. He is a hard worker and as conscientious a delegate as the American Medical Association possesses.
  3. The change in locale of the annual meeting of the American Medical Association for 1948, 1949 and 1950. In 1948 the change will be to Chicago instead of St. Louis. In 1949 Atlantic City instead of New York. In 1950 it will be San Francisco.
  4. The supplementary meeting of the House of Delegates in mid winter not necessarily to be held in Chicago but in various centers changed each year. Two-day sessions to be followed (as stated previously) by two-day scientific exhibit for the general practitioner. Name of the place for the December, 1947, meeting has not yet been determined.
- In conclusion, the meeting of the House of Delegates was most satisfactory one although rather too long drawn-out for reasons given above. The great number of resolutions introduced were fairly and patiently considered and we feel certain as we have in years past that once again we saw in operation a first rate working medical democracy. Our opinion was confirmed by all our foreign guests who spoke on the subject.

DAVID D. SCAMMELL



## APPENDIX NO 9

## COMMITTEE TO STUDY SPECIAL SERVICES

This committee has been asked to define hospital services and medical services and to establish the proper relations between physicians and hospitals.

To gain as accurate an appraisal as possible of the sentiments of the physicians of the Commonwealth on these important problems, a post card was sent to the 6000 participating Blue Shield physicians, requesting their opinion. Fifty-one replies were received. Thirty-four of these expressed the belief that nonmedical hospital services and medical hospital services should be strictly separated. None opposed this separation. Of the remaining 17, the majority complained of their exclusion from hospital staffs and seemed to believe that the solution of this problem constituted part of the committee's function. Although the committee is sympathetic with physicians who are faced with this problem, it considers the problem to be outside the scope of its activities and not implied in the order of the Council establishing its duties.

In attempting its task the committee is well aware of the fact that conditions may properly vary in different localities and in different institutions, that the practice of medicine is undergoing rapid changes under unusual stresses, and that the concepts of tomorrow may vary markedly from those of today.

There are, however, certain fundamental principles that should not change if the profession of medicine is to discharge its obligation to society on an increasingly high level.

First, we accept the principle that the primary object of medical practice is to deliver the best possible care to the patient. Second, we believe that this objective can best be attained by an independent and unfettered profession, conscious of its ideals and its responsibilities.

These principles are basically defined in Chapter III, Article VI, Section 5, of the *Principles of Medical Ethics of the American Medical Association*.

It is unprofessional for a physician to dispose of his professional attainments or services to any lay body, organization, group or individual, by whatever name called, or however organized, under terms or conditions which permit a direct profit from the fees, salary or compensation received to accrue to the lay body or individual employing him. Such a procedure is beneath the dignity of professional practice, is unfair competition with the profession at large, is harmful alike to the profession of medicine and the welfare of the people, and is against sound public policy.

Nothing in this report refers to interns, residents or fellows. The committee is aware that this problem deserves separate consideration.

In accordance with these principles the committee submits the following definitions and recommendations.

## SERVICES RENDERED IN HOSPITALS

*Nonmedical Hospital Services*

Nonmedical hospital services are defined as those services, technical and nontechnical, provided by other than a registered physician, which are required for the care of patients, the making of a diagnosis and the treatment and prevention of disease, and those services rendered by a registered physician in an administrative capacity or as the head of a department when such services do not include the obtaining or interpretation of information in behalf of an individual patient.

These shall be considered to include the following: administration, nursing, social service, record room and library, pharmacy, dietary service, housekeeping and laundry, main-

tenance of building and grounds, including the provision, maintenance, repair and replacement of technical equipment and supplies, provision of technical and nontechnical personnel and their qualified supervision, reports without interpretation from the clinical laboratories, and such other services as may be necessary for the operation of a hospital.

*Medical Hospital Services*

Medical hospital services are defined as services other than administrative, rendered by a registered physician directly or indirectly to or in behalf of an individual patient for the obtainment and interpretation of data, including consultation and advice, for the diagnosis, treatment and prevention of disease. Such services will embrace the general and special practice of medicine, surgery and obstetrics, and the practice of the related specialties including anesthesiology, physical medicine, radiology, pathology and clinical pathology including bacteriology, clinical chemistry and other clinical laboratory specialties.

It is accepted as a basic principle of good medical practice that a professional interpretation should accompany the report on radiologic examinations and on materials and tissues examined by the pathologist.

## ESTABLISHMENT OF PROPER RELATIONS BETWEEN PHYSICIANS AND HOSPITALS

To establish principles governing the proper relations between physicians and hospitals, your committee makes the following recommendations:

That the medical costs of hospital care be separated from the nonmedical costs, as can be done by existing and accepted methods of cost-accounting, and that they appear thus separated on the statement submitted to the patient.

That bills for all medical services be rendered in the name of the physician or physicians performing the services.

That a basic principle in the establishment of charges should be that each department be self-supporting. This principle should be so applied that neither the hospital nor the physician rendering the service will exploit the patient or each other.

That fees for medical services collected by the hospital be established by joint action of a representative committee of the staff and the governing body of the hospital and including also the head of the department and the administrator.

That the basis of financial arrangement between hospital and physician may be salary, commission, fees, or such other method as will best meet the local situation, with due regard to the needs of the patient, the community, the hospital and the physician.

It is the opinion of the committee that acceptance and practice of these principles will clarify the confusion that now exists regarding responsibility for the payment of medical hospital services and nonmedical hospital services, as defined above, by prepayment and other insurance plans.

In conclusion, the chairman wishes to record the fact that during the period of its intensive labors, holding prolonged meetings under adverse weather conditions, the committee averaged 90 per cent attendance. He wishes also to express the appreciation of the committee to those consulting advisers and others who have given so freely of their time: the president of the Society, Dr. Edward P. Bagg and the president-elect, Dr. Daniel B. Reardon, Drs. Allan M. Butler and Vlado A. Getting, of the Committee on Medical Economics, Dr. John F. Conlin, director of medical information and education of the Massachusetts Medical Society, and Dr. Nathaniel W. Faxon, substituting for Dr. Charles F. Wilinsky at the final meeting.

# CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

## Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

## CASE 33491

### PRESENTATION OF CASE

A seventy-one-year-old night watchman entered the hospital complaining of pain in the epigastrium and chest.

He had always been in good health until six weeks before entry, when he began to have epigastric distress, which he described as a vague soreness or feeling of pressure. This was not related to meals or other activities. During the following few weeks his appetite fell off, and he grew progressively weaker. The epigastric distress became more marked and more like pain in quality. This pain did not radiate. Two weeks before admission rather severe pain developed in the lower portion of the chest on both sides, which was definitely aggravated by coughing and deep breathing and relieved somewhat by lying on the right side. The pain often radiated to the left shoulder and axilla but was also felt at times in the right axilla. The patient denied fever or chills. There had been no nausea, vomiting or evidence of blood in the stools. The bowels moved normally until the week prior to admission, when the food intake decreased markedly. He had lost 15 pounds in weight during this illness.

Physical examination revealed a well developed, slim man who appeared chronically ill. He complained of an inconstant pain in the left shoulder and epigastric soreness. There was obvious distress on cough and inspiration. The chest showed poor expansion and was somewhat increased in the antero-posterior diameter. There was slight dullness in the left upper portion of the chest, and the breath sounds in the lower left portion were decreased. The diaphragmatic descent on both sides was poor. The heart was of normal size, with regular rhythm and no murmurs. There was slight distention of the abdomen, with tenderness and spasm in the epigastrium. High in the epigastrium, 5 cm below the xiphoid process, an ill defined, hard, tender mass was palpable. This seemed to pulsate, and over it a soft to-and-fro souffle was heard. Liver dullness extended about 2 cm below the costal margin. The

prostate was diffusely enlarged to about twice the normal size.

The temperature was 100.6°F, the pulse 66, and the respirations 28. The blood pressure was 125 systolic, 50 diastolic.

X-ray studies showed no abnormality of the esophagus, stomach or duodenum. There were a few diverticula in the sigmoid. No abnormal soft-tissue masses or calcifications were noted in the abdomen. Pyelograms disclosed good excretion of dye by both kidneys, without deformity of the calyces. A chest film revealed a small amount of fluid in the right pleural sinus and an area of increased density within the lung in the left pleural sinus. The heart was normal in size and shape. The aorta was not unusual. No shadow representing the gall bladder was demonstrated by Graham test.

Examination of the blood revealed a red-cell count of 2,750,000, with a hemoglobin of 9 gm, and a white-cell count of 7800, with 72 per cent neutrophils. Urinalysis demonstrated a specific gravity of 1.017, a + test for albumin and no sugar. The nonprotein nitrogen was 48 mg per 100 cc, the total protein 6.13 gm, the albumin 3.94 gm, the globulin 2.19 gm, the calcium 8.8 mg, and the phosphorus 3 mg per 100 cc, the serum amylase was 63 units, and the phosphatase 3 units. The van den Bergh reaction was 0.2 mg per 100 cc direct and 0.4 mg indirect. The prothrombin time was 22 seconds (normal, 19 to 20 seconds). Three stools were guaiac negative.

During the patient's stay on the ward his condition remained unchanged for the first ten days. He continued to complain of epigastric pain. To some observers the epigastric mass seemed to have increased slightly in size during that period. In addition redness and tenderness were noted along the course of the left superficial saphenous vein. A review of the chest films showed multiple areas of increased density, some of which were linear in both lung fields.

On the twelfth hospital day the patient complained of severe pain under the left costal margin, which radiated up the side of the chest. Coughing and deep inspiration caused severe pain in this area. Later that day he became extremely weak and cyanotic and vomited 200 cc of normal-appearing gastric contents. This was followed by unconsciousness and two generalized convulsions. He regained consciousness for a brief period, but a short time later gradually became comatose and expired.

### DIFFERENTIAL DIAGNOSIS

DR. F. DENNETTE ADAMS: We have two distinct types of pain to explain: soreness or distress in the epigastrium soon developing into pain and, a month later, what appears to have been a new or different episode, located in the chest and aggravated by breathing and coughing. Although they may have originated from the same source, I believe that they

did not, it therefore seems wise to consider them separately

Occurring in a seventy-one-year-old man, the epigastric pain coupled with loss of appetite, increasing weakness and, what is very important, rapid loss of weight is most suggestive of malignant neoplasm. Quite properly, one first suspects the stomach. But considerable doubt is cast on this suspicion by the rapidity with which the illness developed and the absence of pain-to-food relation. Often in gastric carcinoma, because of ulceration, partial obstruction or interference with normal motility, pain is increased or decreased by eating. Failure of the roentgenologist to demonstrate a lesion also directs attention away from the stomach, although it by no means excludes disease in this organ.

DR WALTER BAUER May I interrupt at this point to say that this pain was rather constant?

DR ADAMS Did it go into the back?

DR BAUER I do not remember, I think not. But the constancy of the pain should be borne in mind. It was not related to meals. It was present all day and whenever the patient awakened at night.

DR ADAMS The easily palpable mass in the epigastrium points to a malignant tumor. But the picture is confused by the added facts that the mass pulsated and that, over it, a souffle could be heard. A highly vascular tumor might produce a souffle, I doubt if it would pulsate. These two signs taken into consideration with the character of the pain, emphasized by Dr. Bauer, demand consideration of abdominal aneurysm. In my opinion, however, the other symptoms, notably rapid loss of appetite, weight and strength, exclude this diagnosis. The pulsation and souffle must be discounted — one can explain them on the basis of transmission from the aorta as a result, perhaps, of pressure on the vessel by the mass itself.

The laboratory findings are not especially helpful. The anemia, with the history and stool examinations tending to exclude alimentary-tract bleeding, is consistent with cancer. The slight elevation of blood nonprotein nitrogen could have been caused by recent starvation and dehydration. The slightly increased serum amylase (54 to 55 units is to be regarded as top normal) may or may not have been significant. At least, it is not inconsistent with the diagnosis I propose to make.

I cannot get away from the speed with which the illness developed. The pain in the epigastrium and the rapid loss of weight and strength must have been due to a malignant lesion. The disease most likely to cause them in so short a period is cancer of the pancreas. I know of no other that, once it takes hold, will pull a patient downhill more quickly. The mass, the elevation of serum amylase and the negative gastrointestinal x-ray examinations can be regarded as important supplementary or confirmatory signs, as can the disturbance that I will

discuss in connection with the pain in the chest. Lymphoma should always be mentioned. This man could have had a lymphoma, but there are no special hints in the picture. The mass conceivably could have been the gall bladder, but I doubt it. We have no filling on the dye test. Perhaps autopsy will show a few small stones or a chronically diseased gall bladder, but if so, these findings will be incidental. The gall bladder could have been normal. Certainly, the primary cause of the illness was not in that organ.

We must now turn to a consideration of the pain in the chest — thus far disregarded but by no means forgotten. Repeated attacks first on both sides then on one or the other, often with extension into the shoulders or axillas and with aggravation by deep breathing. In a chronically ill person of this age, such attacks are almost certainly due to pulmonary embolism, irrespective of what can be seen by x-ray study. Even if the physical and roentgenologic examinations of the lungs were entirely negative, or if I were forced to make a diagnosis without benefit of x-ray film, I would come out flat-footedly with one of pulmonary embolism. Another important bit of evidence should be mentioned, it tends to confirm both primary and secondary diagnoses. It is well established that carcinoma favors the development of thrombophlebitis, and of the various carcinomas, that of the pancreas is the one most likely to do so. We have evidence of thrombophlebitis of one saphenous vein, even if no such signs could be demonstrated, I would still make the diagnosis.

May we see the x-ray films?

DR TOUFIC H. KALIL In the chest films an area of increased density is apparent in the region corresponding to the base of the left lower lobe, and the fluoroscopist seemed to think that this lesion was in the lung itself. These are linear areas of increased density that extend from the hilar region to the right lower lobe and the left lower lobe behind the heart, consistent with old, healed infarcts on the right and on the other side consistent with fresh infarction. So far as the abdominal condition is concerned, I do not see any outline of a soft-tissue mass except in the lateral film of the stomach. There may be some pressure on the posterior wall. Ordinarily, with carcinomas of the pancreas, particularly those in the head of the pancreas, there is widening of the duodenal loop. I do not see any in these films.

DR ADAMS With carcinoma of the head of the pancreas, we would also expect to find jaundice. If my reasoning is correct, the lesion will be found in the body of the pancreas.

The terminal episode seems typical of a large pulmonary embolism. Another severe pain in the side, again with extension upward and aggravated by breathing and coughing, was undoubtedly pleuritic and probably diaphragmatic, later, cyanosis and unconsciousness occurred, followed by death. The

cyanosis is typical of a large pulmonary embolism, the spells of unconsciousness one can explain on the basis of temporary cerebral anoxia due to the circulatory insults. If death had been due to rupture of an abdominal aneurysm, abdominal or back pain or both would have been intensely severe, the picture of shock would have developed, cyanosis would not be striking, and the very last episode would have been longer — probably half an hour to a few hours.

Perhaps I am vulnerable in discounting the pulsation and the soufflé related to the mass and the failure of the gall bladder to fill with dye, but the other features of the case are so convincing that they force me to the diagnoses of carcinoma of the body of the pancreas, multiple thrombophlebitis, and multiple pulmonary embolism and infarction.

Dr. TRACY B. MALLORY: Dr. Bauer, will you tell us your impression?

Dr. BAUER: I thought that the patient had carcinoma of the pancreas. I must admit that when I first examined him I did feel this pulsating mass. From the time it was noticed the question was raised repeatedly whether or not we were dealing with an aortic aneurysm. Dr. Levine, who made the ward visit with me one day, favored that diagnosis. I thought that the nature of the pain itself was much more in favor of cancer of the pancreas, and I adhered to that. I was in error in the beginning when I interpreted the chest pain as part and parcel of one disease. Subsequent events left no doubt that the cause of death was pulmonary embolism.

Dr. FRANCIS D. MOORE: Is it not worth while observing that carcinoma behind the head of the pancreas can coexist with a palpable mass and not produce jaundice, a space-occupying lesion away from the ducts? Is it not notoriously a silent disease? Here was a man with pain that was bothering him a great deal, — rather sharp pain, — and as I listened to the story it sounded more like a vascular pain than a retroperitoneal pain.

Dr. BAUER: I did not think so as I saw him. In fact, this mass was not so impressive as might be gathered from the record. I thought that a slight compression of the abdominal aorta was responsible for the bruit that was heard.

Dr. ADAMS: I reasoned the way you did, Dr. Moore — but came up with a different conclusion: the tumor had been growing, silently perhaps, for a long time, but once it announced its presence, rapid decline of the patient occurred. This is my conception of the pattern usually followed by carcinoma of the pancreas. I do not see why a patient with aneurysm should go downhill so rapidly.

Dr. MOORE: Why not? He could have had a palpable, pulsating mass that came apart as it dissected along in new areas.

Dr. ADAMS: Possibly. But the 3 cases of abdominal aneurysms that I can recall at the moment have not shown constitutional manifestations such as

those that were predominant in this case. The patient had pain, — in front or in back, — but that is all until serious rupture occurred.

Dr. BAUER: It is a peculiar story for dissecting aneurysm. It was not intermittent pain. So far as I could ascertain the pain was present constantly twenty-four hours around the clock with no history of an initial episode of severe pain with associated shock followed by a period of relative freedom and then recurrence. It was not that type of story.

Dr. BENJAMIN CASTLEMAN: Pulsation is not observed with dissecting aneurysm, it occurs only with a saccular aneurysm.

Dr. BAUER: The question was whether or not it had dissected.

#### CLINICAL DIAGNOSES

Carcinoma of pancreas  
Pulmonary infarcts, multiple.

#### Dr. ADAMS'S DIAGNOSES

Carcinoma of pancreas  
Multiple thrombophlebitis  
Multiple pulmonary embolism and infarction

#### ANATOMICAL DIAGNOSES

Carcinoma of body of pancreas  
Thrombophlebitis of leg veins  
Pulmonary embolism and infarctions, multiple  
Diaphragmatic pleuritis  
Arteriosclerosis, generalized  
Cardiac hypertrophy, slight.

#### PATHOLOGICAL DISCUSSION

Dr. MALLORY: At post-mortem examination we found a large tumor mass arising from the body of the pancreas. The head and tail were free. The tumor had metastasized rather extensively to the regional lymph nodes, especially the retroperitoneal nodes, and a number of large nodes were found almost completely surrounding the aorta, which may have been compressed to some degree. There were scattered metastases in the liver as well.

The major pulmonary arteries showed no embolus, but when the small arteries in the lung were dissected, emboli were found in nearly every branch in both lower lobes and in the right middle lobe. These had resulted in infarction, whereas in the upper lobes emboli were also present but had not caused changes in the lungs. It is therefore likely that the terminal episode was the final embolic occlusion of the last patent arteries in the two upper lobes. The entire diaphragmatic pleura of both lower lobes and the superior surface of the diaphragm were covered with thick, fibinous exudate about 2 mm thick. There is always some degree of pleuritis associated with pulmonary infarction, but it is relatively unusual to see such a thick, dense exudate as was present in this case.

The other findings were essentially incidental. There was severe arteriosclerosis of the abdominal aorta but no aneurysm or dilatation. There was a moderate grade of vascular nephritis, as well as a slight degree of cardiac hypertrophy, but nothing else of significance.

DR ADAMS: What about the gall bladder and bile ducts?

DR MALLORY: They contained no stones.

DR ADAMS: Did the patient have thrombosis throughout the vein, which I rather associate with cancer of the pancreas?

DR MALLORY: He had extensive thrombosis of the saphenous system and the deep veins in the calves of both legs.

DR MADELAINE BROWN: Was the brain examined?

DR MALLORY: No.

DR ADAMS: Three features of this case, in my opinion, cannot be emphasized too often. The first is the normal gall bladder, failure of the gall bladder to fill with dye does not always indicate gall-bladder disease — a fact frequently disregarded by clinicians and roentgenologists. The second consideration is the minimal signs of extensive thrombophlebitis, and the third the paucity of physical and x-ray signs in the lungs in the presence of extensive embolic disease. The diagnosis of embolic disease of the lungs must be made on the basis of history, backed by a knowledge of when and why it is likely to occur.

### CASE 33492

#### PRESENTATION OF CASE

A sixty-nine-year-old jeweler was admitted to the hospital complaining of paralysis of the legs.

Six months prior to admission he began to experience pain high in the back, radiating around to the axillas and pectoral regions and severer on the left. Two weeks before entry he began to have numbness of the feet that had gradually extended upward to the legs and abdomen and, several days before entry, weakness, which rapidly progressed to paralysis of the legs. For the past two days he had experienced difficulty in voiding. There had been no headaches, vomiting, speech difficulty, dizziness or abnormal smell or taste. There was no history of convulsions or loss of consciousness.

There was a history of syphilis forty years before admission.

On physical examination the bladder was palpable several centimeters above the symphysis. There was complete paralysis of both legs. The arm jerks were normal, the abdominal reflexes were absent. The knee jerks were active, and the ankle jerk was absent on the right and weak on the left. The plantar reflexes were extensor. Pain and temperature sensibility were reduced below the third rib. Touch stimuli of medium intensity were felt on the chest and abdomen but not on the legs, and

vibratory sensation was lost below the lower sternum. There was a nontender kyphus or prominence of the upper thoracic spine. The right lobe of the prostate contained a firm, slightly irregular mass.

The blood pressure was 128 systolic, 82 diastolic.

Examination of the blood revealed a hemoglobin of 16 gm and a white-cell count of 21,600. The specific gravity of the urine was 1.010, the sediment contained rare red and white cells. X-ray films of the chest showed a complete collapse of the third thoracic vertebra, with slight wedging of the body of the second. No definite soft-tissue mass was seen in this region. The collapse was apparently due to destruction of the body of the vertebra. Slight pleural thickening was seen at the base of the right lung, the aorta was sclerotic and tortuous, the heart was within normal limits.

On admission a spinal tap revealed an initial pressure of 0, with no response to jugular compression, 12 lymphocytes per cubic millimeter and a ++ Pandy reaction. Pantopaque introduced at the third lumbar vertebra was arrested opposite the lower margin of the third rib. No cap was observed.

An operation was performed on the day of admission.

#### DIFFERENTIAL DIAGNOSIS

DR AUGUSTUS ROSE: May we see the x-ray films?

DR TOUFIC H. KALIL: The involved vertebra is entirely collapsed and disintegrated. On each side there is a fairly good joint space remaining. Immediately in front of the involved vertebra there is a little soft-tissue swelling.

DR ROSE: Do you see any other evidence of bone involvement?

DR KALIL: No, I do not. The second thoracic vertebra looks fairly good.

DR ROSE: What about the lung fields? Would you say that they are sufficiently clear to rule out x-ray evidence of metastatic disease?

DR KALIL: Yes, they are.

DR ROSE: What about the thickening of the pleura? Is that significant?

DR KALIL: Merely of old disease, especially at the right base and right apex, with a few linear areas of density extending into both apices.

DR ROSE: There is no active disease, but some soft-tissue swelling around the vertebrae, and I suppose you will agree that it is a bone destruction of the body of the vertebra.

DR KALIL: It seems so, unless it is an old fracture that has finally become decalcified, which might possibly give the same appearance.

DR ROSE: This was a sixty-nine-year-old man who had had pain in the upper portion of the chest for six months. Two weeks prior to admission, he developed a transverse myelitis. Evidence, particularly that of a spinal puncture, demonstrated that the myelitis was probably due to compression. The patient was promptly operated on. Generally, a

patient with compression myelitis should be operated on as quickly as possible, irrespective of the diagnosis. It has been variously estimated that if spinal cord is mechanically compressed for longer than six to eight hours, recovery is unlikely. Compression produces ischemia. Accordingly, in this patient operation was indicated as an emergency procedure—even though the surgeon very probably had fewer data for diagnosis than we have.

Before considering the various possibilities let us think of the myelitis. The myelitis was not complete. Touch was still felt on the chest and abdomen, although it was not felt on the lower extremities. Some impulses were passing through the compressed area of the spinal cord. The history of pain before the development of paralysis points to irritation of nerve roots, at the level of the third thoracic segment, as in a case of fractured vertebra or pressure from extramedullary tumor. Furthermore, the ascending paralysis with sensory loss is characteristic of an increasing compression of the spinal cord. Complete flaccid paralysis is consistent with compression of the cord, even though the plantar reflexes are extensor. The sensory level points to the level of the lesion. Loss of pinprick or temperature sensation is much more usual from any type of spinal-cord disorder than loss of touch sensation. The tendon reflexes in this case were different from what is expected in a rapidly developing transverse lesion of the upper thoracic cord. With Babinski signs, very active tendon reflexes are usually found. The absence of one ankle jerk and the reduction of the other raise the question of some other neurologic condition, possibly antedating the cord compression. Since we have the history of syphilis we ought to take that into consideration.

We then come to the differential diagnosis of the etiology of the compression. From the destruction of the body of the third thoracic vertebra, the kyphosis, the sensory level and the other neurologic findings, we must assume that the spinal-cord disease was at the level of the third thoracic vertebra. The Pantopaque examination showed no cap formation, the contrast medium was arrested at that level.

What conditions cause destruction of the body of the vertebra and secondary spinal-cord pressure? The first, of course is Pott's disease, or tuberculosis of the vertebra, of which there is no evidence in this case. Primary tumor of bone should come next in consideration but would have caused some distinctive features visible in the x-ray film.

Metastatic disease and syphilis are next in importance. Taking syphilis first, I believe that the history forty years previously may be significant. We are not told about the pupils.

Dr. CHARLES S. KUBIK: I believe that they were normal.

Dr. ROSE: The absence of one ankle jerk and the sluggish character of the other, in the presence of transverse myelitis, might be taken as evidence that

the patient had at least had neurosyphilis. Normal pupils make this less likely. Even if he had had neurosyphilis, other factors are necessary to explain the present illness. He could have had a gumma of the vertebral body, but again the gummatous lesions of the vertebra have distinctive features on x-ray study and are not usually confined to the body of one vertebra. Could the lesion have been a Charcot joint, with a compression fracture? Again, there would have been definite x-ray evidence, with bone proliferation and involvement of at least two vertebrae. Charcot joints of the spine are more often found in the lumbar, weight-bearing joints than in the upper thoracic portion of the spine. Before syphilis is discarded, one must mention gummatous involvement of the spinal dura, which is uncommon but is found in the lower cervical region and may give signs and symptoms of spinal-cord and nerve-root compression.

The rectal examination detected a nodular, slightly irregular firm mass in the prostate. Prostatic carcinoma is prone to metastasize to bone, especially the vertebrae. It is therefore possible, and I put as my first diagnosis a vertebral metastasis. The spinal-cord compression was secondary to a pathologic fracture of the diseased vertebra. I do not believe that syphilis played an important role in the present illness.

A PHYSICIAN: Is there any interpretation of the soft-tissue tumor lying opposite the lesion of the eighth to twelfth thoracic vertebrae?

Dr. ROSE: I believe that that is the descending aorta, which is tortuous.

#### CLINICAL DIAGNOSIS

Extradural upper thoracic spinal tumor

Dr. ROSE's DIAGNOSIS

Carcinoma of prostate, with metastasis to spine

#### ANATOMICAL DIAGNOSIS

Carcinoma of prostate, with metastasis to spine

#### PATHOLOGICAL DISCUSSION

Dr. WILLIAM SWEET: This man was operated on under local anesthesia because he had almost complete paralysis of the intercostal muscles. The fluid in the bronchi and lungs could not be raised when he attempted to cough. A laminectomy was carried out on the upper three thoracic vertebrae and disclosed reddish tissue suggesting neoplasm not only posterior to the dura but also on both sides and anterior to it. Before the lateral and anterior portions of the neoplasm were attacked the pedicles were removed to permit dissection in a direction always away from the dura and the spinal cord. It adds further stress to the operation in these cases to remove the pedicles, but I have been doing this because my results following laminectomy only have

been uniformly poor in patients with extradural malignant neoplasm who have developed a transverse lesion of the thoracic portion of the spinal cord. In this case a considerable mass of tissue suggesting neoplasm was encountered on the right side of the dura at the level of the second and third thoracic vertebrae. The bone of the vertebral bodies anteriorly was also grossly abnormal, and the prognosis for recovery of power in the legs was consequently poor. The postoperative course has thus far borne this out. The patient has recovered appreciation of touch, pinprick and temperature in the lower extremities, but there has been no suggestion of recovery of motor power.

DR KUBIK. I saw the patient when he was admitted. It seemed quite certain, even without a myelogram, that there was compression of the spinal cord. The level was fairly definite, and metastatic carcinoma seemed the most likely possibility. I thought, as Dr. Rose did, that whatever the lesion might be, immediate decompression of the cord was indicated.

This was a carcinoma of the prostate, with metastasis to the spine, which was responsible for the paralysis. As Dr. Sweet has pointed out, our experience here has been that when paralysis is as severe as it was in this case the prognosis is very nearly hopeless, particularly when the paralysis

develops suddenly or very rapidly. It is important to point out that this patient had pain in the chest and back, with radiation anteriorly, for a number of months before he developed any other neurologic symptom. It is more than likely that a diagnosis could have been made much earlier and compression of the spinal cord prevented. In 1942 we had a patient here with carcinoma of the prostate and metastasis to the lumbar spine, as well as with marked weakness of the legs, complete spinal subarachnoid block, xanthochromic fluid and a high protein below the block. Under treatment with stilbestrol the compression of the cauda equina was relieved, the paralysis cleared up, and the patient returned to work. He was all right four years later. We have heard that he was recently admitted to another hospital, presumably because of a recurrence of the metastases.

DR ROSE. Do you suppose that stilbestrol at the time of the last admission would have been of any value, in the presence of collapsed vertebrae and compression on a mechanical basis?

DR KUBIK. I think that the outlook is thoroughly poor but that the treatment should be tried. There was, as you pointed out, some sensation at the time of operation, indicating that transection of the spinal cord was not quite complete.

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## INFLUENZA

Most of the epidemics of influenza that have occurred in New England during the past few years have had their peak of incidence during the months of December and January. Those in which studies have been made here, as elsewhere, have been proved to be due to influenza virus—either influenza A or B. Vaccines containing strains of these viruses are now available commercially and have been used to a certain extent in the last three or four years in attempts to prevent the disease. At this time, therefore, many physicians and other interested individuals and groups are naturally raising the question of the value of such vaccines and whether or not they should be employed.

A comprehensive and critical review of the present status of the influenza problem is contained in this issue of the *Journal*. A report of the Study Com-

mittee on Vaccination Against Influenza of the American Public Health Association has also been published recently<sup>1</sup> and at least two preliminary reports on the experiences with vaccination against influenza in 1947 are also available.<sup>2,3</sup>

One of the important epidemiologic features that has recently been stressed concerning influenza is the apparent periodicity of epidemics of this disease.<sup>4</sup> This theory seems to permit the prediction within certain limits that an influenza epidemic will occur in any given year, as well as the type of influenza virus that is likely to be responsible for that epidemic. On the basis of a two-year to three-year cycle for influenza A epidemics and a four-year to six-year cycle for influenza B, an epidemic of the latter type was expected and materialized during the winter of 1945-46. There were at least 2 chances out of 3 that influenza A would occur during the same year and if it did not occur during that year, it was almost certain to occur the following winter.

Two events have transpired that, although they do not necessarily upset the fundamental theory, were somewhat disconcerting. In the first place, cases of influenza A were identified in several widely scattered areas either at the time of the influenza B epidemic or shortly thereafter.<sup>5,6</sup> Secondly, an epidemic occurring in many parts of this country during the winter and early spring of 1947 was due to influenza A.<sup>2,3</sup> It is by no means clear that these two outbreaks of influenza A in successive years were sufficiently widespread to be of significance in relation to the basic cycles of the influenza epidemics in this country. The most recent of these outbreaks, however, was disturbing in addition because of the fact that no definite protection was afforded to groups of persons who had been given vaccines containing influenza A and B during the months preceding that outbreak. This failure was in sharp contrast to the fairly good results obtained from vaccination during the influenza A epidemic of 1943-44 and the still better effects reported from immunization with A and B vaccine during the influenza B epidemic of 1945.<sup>1,2</sup> The failures in 1947 proved to be due to a marked antigenic difference between strains of influenza A responsible for the 1947 epidemic when compared with the strains that had caused previous outbreaks.



Two of the strains from the earlier outbreaks had been incorporated in most of the vaccines that were available at the time

From these experiences it seems that the problem of influenza vaccination at the present time is by no means entirely solved. It also appears that unless the recent occurrences of influenza A were spurious or sharply limited, no widespread epidemic of either influenza A or B is to be anticipated in this country during the present winter. However, as pointed out in Dingle's review, further observations are necessary to test the validity of the theory of the periodicity of influenza, particularly in view of the antigenic differences among influenza viruses of the same type. Additional large-scale studies of the efficacy of influenza vaccination are also needed both in view of these differences and because of other factors concerned with the protective value of various types of vaccines.

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#### "AN ADVENTURE IN CO-OPERATION"

THE sixth annual New England Postgraduate Assembly, held on the last three days of October, 1947, at the Copley Plaza Hotel in Boston and sponsored by the medical societies of the six New England States, broke all previous records for attendance. Over 700 physicians from Eastport, Maine, to Stamford, Connecticut, were registered, in addition to one each from California, Illinois and New Jersey, eight from New York and six from Canada. The program, previously announced to the medical profession of this section through the medium of these pages, was well selected and varied, the speakers, coming from major medical centers of the country, delivered their addresses ably and were appreciatively welcomed.

The dinner speaker on October 30, Dr George Baehr, president of the New York Academy of

Medicine, presented his views on the continuing education of physicians to an audience of nearly one hundred and fifty. Dr Baehr emphasized the changes that thirty years of scientific discovery have made in the training of the physician, dwelling particularly on the point that success in private practice can no longer be accepted as the criterion for a teacher. The quickened step of time in its march must be matched with new standards on our part—full-time clinical hospital chiefs, improvements in rural hospitals and a greater awareness of the responsibilities they owe to their communities, private-practice groups designed to fit in with the facilities of the community hospital and plans for prepaid medical care that are just rather than compulsory.

The real contribution of the Assembly, however, was the assurance it gave of success in the co-operative venture upon which the state medical societies of New England have embarked. Many of our problems are similar, and we can bring our varied experiences with them to bear on their solution. Others are unique for the background against which they are viewed, whether of rural Vermont or of industrial Rhode Island, and we can enrich our own knowledge by a little intermingling of it with that of our neighbors.

This desire for mutual improvement without other than healthy competition reflects the best of our sectional heritage and our pride in the particular homeland that we inhabit. Even as we take counsel with ourselves, however, to better our opportunities and improve our professional output, we are conscious of no antagonism to other sections of the country less fortunate than New England. Rather are we willing to share our benefits, to accept a moral and intellectual leadership, if necessary, to leaven the whole loaf.

#### MASSACHUSETTS MEDICAL SOCIETY BUREAU OF CLINICAL INFORMATION

All secretaries of various medical groups, such as special societies and alumni associations, are requested to notify the Bureau of Clinical Information regarding scheduled meetings, annual dinners and so forth. If such data are on file, it is hoped that duplication of dates can be avoided.

## DEATHS

**AVEDISYAN**—Avedis D. Avedisyan, M.D., of Boston, died on November 16. He was in his seventy fifth year.

Dr. Avedisyan received his degree from Tufts College Medical School in 1896.

His widow and a sister survive.

**BEAN**—Charles F. A. Bean, M.D., of Medford, died on July 23. He was in his sixty third year.

Dr. Bean received his degree from Harvard Medical School in 1912. He was formerly house officer of the Malden Hospital and was later a member of the surgical staff of the Lawrence Memorial Hospital, Medford, as well as a censor and counselor of the Massachusetts Medical Society. He was a fellow of the American Medical Association.

His widow survives.

**DELANO**—Samuel Delano, M.D., of New Britain, Connecticut, died on November 8. He was in his ninetieth year.

Dr. Delano received his degree from Harvard Medical School in 1883.

**HENDERSON**—Francis F. Henderson, M.D., of Milton, died on November 20. He was in his sixty second year.

Dr. Henderson received his degree from Tufts College Medical School in 1911. He was surgeon-in-chief, Fourth Surgical Service, Boston City Hospital, and a fellow of the American Medical Association.

His widow, two brothers and a sister survive.

**SIBLEY**—Benjamin E. Sibley, M.D., of Brookline, died on November 19. He was in his seventy fourth year.

Dr. Sibley received his degree from Harvard Medical School in 1905. He served for more than thirty years as chief medical officer for the Boston Elevated and Metropolitan Transit Authority and was formerly a member of the medical staffs of Liberty Mutual Insurance Company and Massachusetts Institute of Technology. He was a fellow of the American Medical Association.

His widow, two daughters, four grandchildren and a sister survive.

## MEDICOLEGAL ABSTRACT

**Hospitals—Whose servant is the intern?**  
On the principle that a charitable institution should be just before it is generous, many states hold charitable hospitals liable for the negligent acts of their servants. No liability is imposed for negligent acts of such persons as physicians and technicians when the hospital has not been negligent in their selection or retention. Cases imposing liability have been those concerning employees such as elevator operators, ambulance drivers, ward attendants and ministerial and administrative workers. An interesting question arises concerning the exact status of an intern—a graduate physician, but usually employed by the hospital. A recent Tennessee case involved that problem.

A pay patient was admitted to a charitable hospital, where she underwent a serious abdominal operation at the hands of her own surgeon. Shortly after the operation the surgeon ordered the administration of a hypodermoclysis. This was administered by Dr. L., an intern in the employ of the hospital. In a suit to recover damages for the negligent administration of the hypodermoclysis the

plaintiff alleged and testified that the injection on the right leg was made without the application of any preparation to the skin and without the use of gauze between the flesh and the needle, that this injection caused much pain and that forty to forty-five minutes elapsed from the starting of the flow until the return of the intern, and that during that time the area around the needle raised up a little, that the intern then removed the needle and administered a hypodermoclysis to the left leg, which was later without undue pain or untoward results, and that the place on the right leg continued to be painful and on the following morning was swollen and discolored and had a blister about the size of a silver dollar. The patient continued to suffer from this condition up to the time of discharge from the hospital and subsequently underwent a local operation on the right leg, which continued to cause great pain and suffering. A medical witness testified that if the solution had been pure and the equipment free of contamination and if the technic of the intern had been proper there would not have been any injury.

On a motion for a rehearing on appeal the attorneys for the hospital vigorously urged that even if the administration had been negligent the hospital would not be liable for the negligence of the intern. They relied largely on the language of Judge Cardozo in the case of *Schloendorff v. The Society of New York Hospitals* (105 N. E. 92) in which it was stated as follows:

The second ground of the exemption is the relation subsisting between a hospital and the physicians who serve it. It is said that this relation is not one of master and servant, but that the physician occupies the position, so to speak, of an independent contractor following a separate calling, liable of course, for his own wrongs to the patient whom he undertakes to serve, but involving the hospital in no liability if due care has been taken in his selection.

The Tennessee court accepted the fact that it was the duty of the intern to follow the orders of the attending physician but stated:

A patient at the hospital is entitled to the generally accepted services of a hospital including the services of the intern. The intern can make no charge for his services. The patient has no voice in the selection of the intern. There is no contract between them. If the attending physician ordered a hypodermoclysis to be administered to a patient it would be the duty of the intern to give it. It was a part of the services rendered by the hospital by virtue of the relation existing between it and the patient.

The court then cited with approval the holding of the Supreme Court of Florida:

There can be no question but that a hospital is as much liable under the doctrine of respondent superior for the negligence of an intern who is in no wise an independent contractor but a mere employee as it is for that of a nurse under like employment.

It also cited the language of the Supreme Court of Virginia:

The intern is not an independent contractor so far as the patient is concerned. The contract is with the hos-

pital for his service. His service is a part of the numerous duties prescribed by the hospital, and he is selected, employed, directed, supervised and paid by the hospital. In rendering such services they act on behalf of their employer.

Judge Ketchum in dissenting relied largely upon the right to control the conduct of the person doing the wrong. He approved the reasoning of the *Schloendorff* case, saying

The hospital did not undertake to treat the plaintiff, or to furnish her with doctors or nurses, but merely furnished the room she occupied and the usual facilities of the hospital for treatment by her own physician and nurses. Dr. L., the intern who administered the hypodermoclysis, was a graduate physician who had been highly recommended to the hospital as a man fully qualified by reason of his education and skill to perform the duties of an intern, and in administering the hypodermoclysis he was acting under the directions of the plaintiff's own physician and not of the hospital. The hospital gave him no instructions in connection with the administering of the hypodermoclysis, which was an operation requiring the technical skill of an expert physician or nurse, and although it employed him as an intern it had no right to control or direct him as to the manner in which the operation should be performed.

Probably, this recent Tennessee decision does not lay to rest the question "whose servant is the intern?" Nor does it touch upon the problem of the status of the resident, in many hospitals a more advanced stage of internship. Is the intern his own master and solely responsible for his own negligence? Is he the servant of the hospital? If so, then the hospital may be liable. Or is he the servant of a private physician in charge, if any? If so, the physician in charge may be liable. The answer may vary in different states. In Tennessee, as a matter of law, the intern is an employee of the hospital and not the servant of the attending physician, and therefore any suit against the physician for the negligent acts of the intern would be unsuccessful. However, it is conceivable that the practice of the particular hospital regarding the supervision, control and direction of the work of an intern may be decisive. In view of the many decisions exempting hospitals from liability for the negligent acts of qualified specialists on the staff of the hospital, such as x-ray and surgical technicians, another state may well hold that an intern is in the same class as any other physician. (*Sepaugh v The Methodist Hospital*, 202, S. W. [2d] 985, 1946.)

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### THE CHANGING CANCER DEATH RATE

During the twenty-one years of the Massachusetts Cancer Program there has been a yearly increase averaging 130 deaths. About 60 per cent of the increase has been among males and 40 per cent among females. However, when allowance for the aging

of the population was made the rise was limited to the males, and there has been a downward trend among females. Not all types of cancer have contributed to this downward trend, for some have shown upward trends and others have been trendless. The mortality rates for cancer of the stomach, buccal cavity, skin, uterus and liver have downward trends. Cancer of the breast, larynx (female), vulva, vagina, scrotum, bladder, esophagus, kidney (female) and rectum (female) showed no significant trend, whereas an upward trend obtained for all remaining organs. The most pronounced in the upward trend group was cancer of the respiratory organs.

The upward trend of individual sites among males was sufficient to give a total upward trend, among females, the downward trend of individual sites was great enough to make a total downward trend. The change in the trend noted in Massachusetts among females was followed a few years later by a similar drop in other states. The change in the adjusted cancer death rate offers speculation regarding the part that can be attributed to cancer-control activities and other circumstances.

## HOMOLOGOUS SERUM JAUNDICE FOLLOWING BLOOD AND PLASMA TRANSFUSIONS

The risk of transmitting jaundice in plasma has been generally appreciated in this country since the outbreak of jaundice in the United States Army camps in 1942<sup>1</sup> was traced to plasma used in the preparation of yellow-fever vaccine. There have been numerous reports of this disease after blood and plasma transfusions in both Army and civilian practice.<sup>2-4</sup> It has also been transmitted by unsterile syringes at venereal-disease clinics.<sup>5</sup> More recent surveys in New York State<sup>6</sup> and England<sup>7</sup> showed attack rates of roughly 5 and 7 per cent, respectively. In Boston Scheinberg, Kinney and Janeway<sup>8</sup> and Moloney<sup>9</sup> have reported further civilian cases. These reports re-emphasize the necessity of weighing the immediate advantages of blood and plasma transfusion against a possible chance of a later attack of jaundice.

To facilitate follow-up studies, the State Biological Laboratory issues an information card with each unit of blood and plasma distributed. The prompt return of this card with details of the patient's name and address and lot number of plasma used make possible a check for immediate reactions, and is also the nucleus for a further follow-up study four to six months later. Such a study to ascertain the incidence of this disease in Massachusetts is now in progress under the auspices of the American Red Cross, the Harvard School of Public Health and the Massachusetts Department of Public Health.

Where cards have not already been sent in, hospitals are asked to assist the study with the relevant data

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## COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER 1947

## RÉSUMÉ

DISEASES	OCTOBER 1947	OCTOBER 1946	SEVEN YEAR MEDIAN
Chenoid	4	2	1*
Chicken pox	309	4	478
Diphtheria	21	8	17
Dysentery	856	94	84*
Dysentery, bacillary	60	6	3
German measles	51	52	46
Gonorrhea	334	413	413
Grossly maculose	1	1	0*
Lymphogranuloma venereum	0	0	1*
Malaria	4	23	16
Measles	120	508	508
Meningitis, meningococcal	6	5	3
Meningitis, pneumococcal	2	3	1
Meningitis, Pfeiffer bacillus	2	2	2†
Meningitis, streptococcal	0	0	0†
Meningitis, staphylococcal	0	0	0†
Meningitis, other forms	0	0	0†
Meningitis, undetermined	7	4	3†
Mumps	374	173	326
Pneumonia, lobar	68	71	161
Poliomyelitis	6	128	54
Scarlet fever	14	10	10
Syphilis	274	196	456
Tuberculosis, pulmonary	322	390	408
Tuberculosis, other forms	248	247	236
Typhoid fever	19	19	19
Undulant fever	3	1	4
Whooping cough	3	3	5
	461	554	555

\*Three-year median.

†Five-year median.

## COMMENT

Diseases above the seven year median are chicken pox, gonorrhea, malaria, measles, meningococcal meningitis, lobar pneumonia, scarlet fever, syphilis, undulant fever and whooping cough.

With 66 cases of poliomyelitis being reported for October it seems evident that the peak was reached in September when 149 cases were reported.

Although diphtheria is much below the prevalence of October, 1946, it still exceeds the seven-year median. In fact only twice since 1935 has the October figure been so high. With the diphtheria season just beginning a further increase can be expected in communities where immunization is not at a high level.

After a low year in 1946 following the epidemic prevalence in 1945 mumps has maintained an upward trend in 1947. This probably indicates that the disease will be prevalent during the coming season, with the usual peak in March or April.

## GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

Diphtheria was reported from Boston, 9, Cambridge 1, Chelsea 5, Dudley, 1, Foxboro 1; Framingham, 1, Randolph, 1, Revere, 1, Somerville, 1 total 21

Dysentery, bacillary was reported from Chelsea, 3, Malden 1, Waltham (Fernald State School), 2, Wellesley 1, Worcester (State Hospital) 7, Wrentham (State School), 46 total 60.

Hookworm was reported from Templeton 1, total 1. Lymphocytic choriomeningitis was reported from Athol 1, total, 1.

Malaria was reported from Medford, 2, Woburn 1, Worcester, 1 total, 4.

Meningitis meningococcal, was reported from Boston, 2, Newton, 1; Quincy 1, Waltham, 1, Westfield, 1 total, 6.

Meningitis, Pfeiffer bacillus, was reported from Wellesley, 1, Worcester 1 total 2.

Meningitis pneumococcal was reported from Cambridge 1, Lawrence, 1, total, 2.

Meningitis undetermined was reported from Springfield, 1, Worcester, 1, total, 2.

Poliomyelitis was reported from Attleboro, 1, Boston 3, Cambridge, 3, Chelsea 1, Chicopee, 1, Concord 1, Dedham 1, Easton, 2, Everett, 1, Falmouth, 1, Fitchburg 2, Gloucester 1, Lawrence, 1, Leominster, 1, Lynn 7, Malden 1, Manchester, 1, Medfield 1, Medford 2, Melrose, 1, Middleboro, 1, New Bedford 1, Newton 4, Quincy, 3, Revere, 2, Saugus 1, Springfield 2, Stoughton 1, Swansea 1, Taunton 1, Wakefield, 2, Waltham, 1, Watertown 1, Wellesley, 7, Williamsburg 1, Woburn 1, Worcester 3 total, 66.

Salmonellosis was reported from Ayer 1, Beverly 2, Boston, 2, Chelsea 3, Ipswich 1, Lowell 1, Marshfield 1, Melrose, 1, Winchester 1, Worcester, 1 total, 14.

Septic sore throat was reported from Boston, 1, Greenfield 1, Haverhill 2, Melrose 1 total, 5.

Trichinosis was reported from Arlington 1, Boston 3, Lakeville, 1, Middleboro, 1, Plymouth 1 total, 7.

Tularemia was reported from Holyoke, 2 total 2.

Typhoid fever was reported from Chelsea, 1, Clinton, 4, Everett, 1, Orange, 1, Worcester 1 total, 8.

Undulant fever was reported from Brimfield, 1, Clinton, 1, Woburn 1 total, 3.

## MISCELLANY

## AMERICAN MEDICAL DIRECTORY

Cards are being sent to all physicians in the United States its dependencies and Canada requesting information to be used in compiling the new *American Medical Directory*. This eighteenth edition the first since 1942, has been long delayed on account of wartime restrictions and the shortage of paper and labor.

Its completeness and accuracy are obviously of vital importance. Any physician who had failed to receive a card by December 1 is urged to write at once to the Directory Department of the American Medical Association requesting a duplicate.

## AWARD TO COLONEI MOORE

Colonel Merrill Moore, of Boston was awarded the Chinese decoration Yen Hui Special Class, on Saturday November 1, at a ceremony held at the quarters of Lieutenant General Albert C. Wedemeyer formerly commanding general, United States Forces China Theater at Fort George G. Meade, Maryland. The decoration was awarded in recognition of outstanding and meritorious service during 1946 while Colonel Moore was on duty as surgeon to the Nanjing Headquarters Command General Peter Pi military attaché to the Chinese Embassy in Washington and formerly aide to the Generalissimo read the citation. The presentation was made by General J. L. Huang of the Chinese Army who was a classmate of Colonel Moore at Vanderbilt University. Colonel Moore had served with distinction in the South Pacific Theater in 1942-1944 and in the Philippines in 1945 prior to his assignment to the China Theater.

## BOOK REVIEWS

*Handbook of Correctional Psychology* Edited by Robert M Lindner, M D, and Robert V Selger, M.D. 8°, cloth, 691 pp New York Philosophical Library, 1947 \$10 00

This book is a veritable safety deposit vault of valuable information. Forty-six experts have co-operated, under the editorial guidance of two able scientists, to bring together the most up-to-date and progressive opinions available concerning the application of psychology to the problem of correcting behavior difficulties. Anyone interested in good government will find this volume worth reading. Its point of view is very broad, but particular problems are given specific attention in the light of common knowledge shared by modern psychiatrists. This is a book that the psychiatrists or social workers will find informative and helpful.

*The Development of Modern Medicine An interpretation of the social and scientific factors involved* By Richard Harrison Shryock. 8°, cloth, 567 pp, with 9 plates New York Alfred A Knopf, 1947 \$5 00

The book, long out of print, was first issued in 1936. It now appears in an enlarged and revised form, brought up to date. The author, a competent general historian, is the leading lay authority on the form of modern medicine now practised in the United States. This thoughtful monograph was widely proclaimed when first published as the best summary of the historical development of medicine in print. The new edition is equally satisfactory. The author handles the more recent controversial matters, such as the programs for socialized practice, the stand taken by the American Medical Association and the pending bills for federal legislation of compulsory health insurance, with great clarity of thought, without aligning himself with any one of the proposals. A particularly well written chapter deals with psychiatry and the impact of Freud on the advance against mental disease. Fully annotated and with a good index, the finely printed volume is a credit to both author and publisher. It is an authoritative text, and the new impression is a welcome addition to the medical literature of our times.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Hospital Care in the United States A study of the function of the general hospital. Its role in the care of all types of illness, and the conduct of activities related to patient service, with recommendations for its extension and integration for more adequate care of the American public* 8°, cloth, 631 pp, with 94 tables and 58 charts New York The Commonwealth Fund, 1947 \$4 50

*Diseases of the Gallbladder and Allied Structures Diagnosis and treatment* By Moses Behrend, M D, consulting surgeon, Jewish Hospital and Mt. Sinai Hospital, and associate in surgery, Jefferson Medical College. With a foreword by Thomas A Shallow, M D, Samuel D Gross, professor of Surgery, Jefferson Medical College. 8°, cloth, 290 pp, with 110 illustrations Philadelphia F A Davis Company, 1947 \$7 00

*The Engrammes of Psychiatry* By J M Nielsen, M D, associate clinical professor of neurology and psychiatry, University of Southern California School of Medicine, and senior attending physician (neurology), Los Angeles General Hospital, and George N Thompson, M D, assistant clinical professor of neurology and psychiatry, University of Southern California School of Medicine and psychiatric consultant, Department of Corrections, State of California. 8°, cloth, 509 pp, with 28 illustrations Springfield, Illinois Charles C Thomas, 1947 \$6 75

*Neuropathology in its Clinicopathologic Aspects* By I Mark Scheinker, M D, assistant professor of medicine (neurology) and instructor in neuropathology, University of Cincinnati College of Medicine, and neuropathologist and attending

neurologist, Cincinnati General Hospital. With a foreword by Tracy J Putnam, M D, professor of neurology and neurologic surgery, College of Physicians and Surgeons, Columbia University, and director of services of neurology and neurologic surgery, Neurological Institute of New York. 8°, cloth, 306 pp, with 208 illustrations Springfield, Illinois Charles C Thomas, 1947 \$6 75

## NOTICES

## ANNOUNCEMENTS

Dr Robert L Mason has returned from military service and is resuming the practice of surgery at 47 Bay State Road, Boston.

Dr Francis Rouillard announces the removal of his office for the practice of obstetrics and gynecology to 1180 Beacon Street, Brookline.

JOSEPH H PRATT  
DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a m

## MEDICAL CONFERENCE PROGRAM

Wednesday, December 10 — The Clinical Significance of Hyperlipemia Dr Robert Holden

Friday, December 12 — Exophthalmos and Proptosis Dr Parker Heath

Wednesday, December 17 — Clinicopathological Conference Drs James M Baty and H E MacMahon

Friday, December 19 — Gastritis Dr Seymour Gray

On Tuesday and Thursday mornings from 9:00 to 10:00 Dr S J Thannhauser will give medical clinics on hospital cases. On Friday afternoons from 2:00 to 4:00 therapeutic conferences will be held with round-table discussion, Dr R P McCombs, Moderator. On the second and fourth Friday afternoons of each month, Dr Merrill Sosman will conduct x-ray conferences from 4:00 to 6:00. On Saturday mornings from 9:00 to 10:00, clinics will be given by Dr William Dameshek. Medical rounds are conducted each weekday except Saturday by members of the Staff from 12:00 to 1:00.

All exercises are open to the medical profession. There will be no conferences from December 24, 1947, to January 3, 1948, inclusive.

## TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet in the auditorium of the Beth Israel Hospital on Wednesday, December 10, at 8:30 p m. Dr Richard H Overholt will speak on the subject, "The Mechanics of Treatment in Pulmonary Tuberculosis."

## GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, December 16, at 8:15 p m. A symposium on recent advances in endocrinology will be presented.

## PROGRAM

The Use of Thiouracil Derivatives in the Treatment of Thyrotoxicosis Dr Mark F Lesses

Radioactive Iodine in the Treatment of Thyrotoxicosis Dr Saul Hertz.

Adrenal Insufficiency Dr Kendall Emerson

Retarded Adolescence. Dr Nathan B Talbot.

## HELEN PUTNAM FELLOWSHIP

The Helen Putnam Fellowship for advanced research in the field of genetics or of mental health will be offered by Radcliffe College for the academic year 1948-1949.

This fellowship, carrying a stipend of \$2000 for an eleven-month period and beginning October 1, 1948, is open to mature women scholars who have their doctorate or equivalent qualifications, and who have research in progress.

Applications should be submitted to Radcliffe College not later than April 1, 1948. The appointment will be announced on approximately May 1, 1948.

(Notices continued on page xxi)

# The New England Journal of Medicine

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## LATE EFFECTS OF TOTAL GASTRECTOMY IN MAN\*

ROBERT M. MACDONALD, M.D.,† FRANZ J. INGELFINGER, M.D.,‡ AND HELEN W. BELDING, M.D.§

BOSTON

**STUDIES** on patients who have survived total gastrectomy for three years or more are few, and contradictory results are reported. For this reason and since total gastrectomy is being practiced with rapidly increasing frequency, we have studied intestinal motor function, intestinal absorption, pancreatic function and the blood picture in 3 patients who have survived total gastrectomy for three, five and ten years, respectively.¶

### CASE REPORTS

**CASE 1.** E. O., a 58-year-old woman was admitted to the hospital with a history of anorexia, weight loss and vomiting of 3 years duration. A total gastrectomy with enteroenterostomy was performed on May 28, 1936. The pathological diagnosis of Dr. Tracy B. Mallory was adenocarcinoma without metastases in the adjacent lymph nodes or extension to the duodenum. One year later when reoperation was necessary to establish a new enteroenterostomy, no evidence of cancer was discovered. Since the second operation, the patient's condition has been excellent, and she has carried on her work as a housekeeper without difficulty. Postoperatively she received liver and iron prophylactically until July 15, 1946.

**CASE 2.** R. V., a 49-year-old Italian was admitted to the hospital with a history of increasing pallor, weakness and anorexia of indefinite duration. For 2 weeks he had felt a mass in the abdomen. On August 20, 1941 a total gastrectomy, splenectomy, subtotal pancreatectomy and enteroenterostomy were performed. The pathological diagnosis of Dr. Mallory was adenocarcinoma. The patient made a moderately good recovery and slowly regained weight. Three years after operation the red-cell count was 4,400,000, with a hemoglobin of 80 per cent. At the end of 5 years, when he was first seen at this hospital, he had lost 10 pounds in weight although he was still feeling moderately well. Blood studies revealed macrocytosis and hyperchromia (Table 1).

**CASE 3.** W. M., a 41-year-old man was admitted to the hospital with a history of intermittent indigestion of 8 years and epigastric pain, poor appetite and weight loss of 4 months duration. X-ray examination revealed an ulcer high on the lesser curvature. Since cancer was suspected total gastrec-

tomy was carried out on August 8, 1943. The pathological diagnosis of Doctor Benjamin Castleman was acute and chronic gastritis with multiple gastric ulcers. The patient was discharged on the 13th postoperative day and remained well for 2 years. He then began to lose his appetite and to feel weak. Pallor was noted and examination of the blood showed a macrocytic, hyperchromic anemia, which responded to injections of liver extract¶ (Table 1). No liver was given after July 9, 1946, but no anemia had developed as of March 17, 1947.

### GASTROINTESTINAL FUNCTION

When the first patient who survived total gastrectomy was studied fifty years ago, it was noted with surprise that she regained her appetite,<sup>22-24</sup> and since then, others have observed that the stomach is not necessary for this sensation.<sup>27-30</sup> All our patients have a normal desire for food and develop hunger. The patient in Case 1 takes three meals a day and only occasionally eats between meals, the meals are of nearly normal size. Another patient (Case 2) has persisted in taking in-between feedings and a bedtime snack. The third patient has to eat irregularly because of his work, but four times a day, on the average, he takes meals about two thirds the size of those consumed before his illness. All 3 patients are on an unrestricted, mixed diet, but take care that the food is well cut and well chewed. Occasionally, they experience borborygmi and mild upper abdominal cramps after eating, and too rapid eating may produce an epigastric sensation of fullness. None of these patients have dysphagia or symptoms suggesting the "dumping syndrome." The weight, although it increased after the operation, has never regained the levels existing before illness.

Fluoroscopic and radiologic examination revealed a normal esophagus and a patent, well functioning esophagojejunal anastomosis. In Cases 1 and 2 the jejunal segment at the anastomosis was dilated, with no mucosal markings except a few thickened valvulae conniventes. The barium meal tended to puddle in these jejunal reservoirs (Fig. 1). In Case 3 jejunal dilatation was not seen. The motor pattern of the lower jejunum and ileum of all 3 patients mani-

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§Assistant in medicine, Department of Medicine, Boston University School of Medicine; fellow in medicine, Robert Dawson Evans Memorial Hospital.

¶These 3 cases were made available through the courtesy of Dr. Reginald H. Smithwick, who has described the operative details elsewhere.

¶These observations were made by Dr. James A. Husted at the Massachusetts General Hospital.

fested minimal to moderate abnormalities of the type seen in the "deficiency pattern" of Golden<sup>31</sup> Films taken five hours after the ingestion of the barium meal demonstrated the opaque medium in the ileum and ascending colon in Case 1 In Case 3, however, the meal was still confined to the small bowel, and in Case 2 only a few jejunal loops were seen, most of the meal still being retained in the jejunal reservoir The twenty-four-hour films showed a normal distribution of the barium meal in all 3 cases

Kymographic records of small-intestine motility were obtained by a method previously described<sup>32</sup>

tain chyme for considerable periods, are prone to develop after total gastrectomy, presumably in an attempt to compensate for the absent reservoir function of the stomach The findings in Case 3, however, suggest that this jejunal dilatation is neither invariable nor apparently necessary

Studies of fat absorption were carried out as follows The patients, who were on a routine hospital diet, ingested between 40 and 60 gm of fat a day An accurate and constant fat intake was not feasible because the subjects, who felt perfectly healthy, did not wish to stay in the hospital for more than a week, and many tests were carried out during that time.

TABLE 1 Blood Findings in Patients Who Lived Three or More Years after Total Gastrectomy

SURGEON	DATE OF OPERATION	AGE	SEX	DIAGNOSIS	ONSET OF ANEMIA AFTER OPERATION	RED CELL COUNT	HEMOGLOBIN	COLOR INDEX
Patients developing macrocytic blood picture					yr	$\times 10^6$		
Dennig <sup>2</sup>	1918	41	M	Ulcer	8	1.4	35%	1.25
Kelly <sup>3</sup>	1939	45	M	Carcinoma	4	2.2	55%	1.25
Marshall <sup>4</sup>	1939	40	F	Lymphoblastoma	7	1.6	7.7 gm	—
Mayo (Hartman <sup>5</sup> )	1917	58	M	Carcinoma	2	—	48-53%	1.2-1.6
Mayo (Weir <sup>6</sup> )	1937	37	M	Ulcer	8	3.22	13.2 gm	—
Meyer <sup>7</sup>	1933	33	M	Gastritis (nonspecific)	5	1.6	55%	—
Pooler and Foster <sup>8, 10</sup>	1926	36	F	Gastritis (? syphilitic)	3	0.5	20%	—
Ransom <sup>11</sup>	1940		F	Carcinoma	4,5	1.6	5.7 gm	—
Ransom (Bethell <sup>12</sup> )	1941	56	M	Ulcer	5	3.6	14.9 gm	—
Smithwick <sup>1</sup>	1941	49	M	Carcinoma	5	2.9	11.0 gm	—
Smithwick <sup>1</sup>	1943	41	M	Ulcer	2	2.06	7.8 gm	1.2
Zollinger <sup>13</sup>	1938	66	M	Carcinoma	8 (6 mo after stopping liver)	1.28	5.1 gm	—
Patients developing anemia of doubtful nature								
Lobenhoffer (Breitenbach <sup>14</sup> )	1922	41	M	Ulcer	6	1.8	39%	1.03
Meyer (Stahnke <sup>15</sup> and Koch <sup>17</sup> )	1931	40	F	Carcinoma	8	2.0-6.0	45-83%	>1
Morrison <sup>16, 19</sup>	1938	68	M	Carcinoma		—	—	—
Moynihan <sup>20</sup>	1907	43	M	Carcinoma	3	—	—	—
Streicher <sup>21, 22</sup>	1932	45	F	Carcinoma	3	—	—	—

The motility records corresponded well with the roentgenologic findings (Fig 2) The jejunum near the anastomosis in Cases 1 and 2 exhibited atony and an absent wave pattern. Only after motility had been stimulated by the ingestion of an egg-nog did motor waves appear The lower jejunum in Cases 1 and 2 and the entire jejunum in Case 3 yielded essentially normal motility records Both radiologic and motility studies of the intestine indicate that large jejunal reservoirs, which may re-

The stools were collected for three days, acidified and dried in toto over a steam bath The dried feces were then finely powdered, and a 10-gm portion was extracted in a Soxhlet apparatus with petroleum ether With such a method, some volatile lipids may be lost, but difficulties encountered with wet methods, such as small, nonrepresentative aliquots and difficult fat extraction, are avoided

When the intake of fat is small, the absolute daily fecal fat excretion is more significant than the pro-

portion of fat output to fat intake, or the percentage of fat in the dried stool.<sup>22</sup> A normal person ingesting no more than 60 gm of fat a day usually excretes less than 5 gm and invariably less than 10 gm in the stools. According to these criteria, the fecal fat excretion of 2 patients was in the high normal range (Table 2), whereas only Case 2 exhibited a frankly abnormal output of fat in the stools. This patient, it will be recalled, had undergone a partial pancreatectomy.

Table 2 also lists the findings of others who have studied fat absorption after total gastrectomy.<sup>14, 23, 24, 25-28</sup> The wide divergence of results is

data, which others have also found difficult to interpret.<sup>21</sup> Nevertheless, even after exclusion of cases that are theoretically subject to criticism, one is confronted, on the one hand, by a patient who a year after operation lost 23 gm of fat<sup>22</sup> and, on the other, by a patient who four years after operation excreted less fat than many a normal person does.<sup>27</sup>

Although an occasional case with frank steatorrhea may be encountered, the data presented in the literature and our own studies indicate that fat absorption is only mildly impaired in patients who have survived total gastrectomy for two or more years. If the fat intake is low, the absolute amount of fat

TABLE 1 (Continued)

MEAN CORPUSCULAR VOLUME 12. MICRONS	MEAN CORPUSCULAR HEMOGLOBIN MICRONS	RED-CELL DIAMETER MICRONS	HEMATOCRIT %	WHITE CELL COUNT /mm <sup>3</sup>	REMARKS
—	—	—	—	40	Blood smear showed nucleated red cells: spinal-cord involvement observed; patient responded to liver therapy but contracted pneumonia and died 9 yr postoperatively
—	—	—	—	—	Blood smear showed macrocytosis and hyperchromia; patient responded to liver and iron therapy and was living 8 yr postoperatively
136	—	—	21.8	47	Blood smear showed nucleated red cells: spinal-cord changes observed; no response to intravenous folic acid, but patient responded to liver therapy and was living 8 yr postoperatively
—	—	—	—	—	Patient had chronic diarrhea: patient died nearly 4 yr postoperatively
—	—	8.1	—	—	Blood smear showed moderate macrocytosis, no megaloblastic changes in bone marrow: liver response not reported: patient living 9 yr postoperatively
—	—	—	—	843	Reticulocyte count 1.2 per cent: blood smear and bone marrow typical of pernicious anemia: no response to extrinsic factor and vitamin C: patient responded to liver therapy but died 6 yr postoperatively
—	—	—	—	115	Patient, who responded to liver therapy: was living 20 yr postoperatively
106	—	—	17.0	245	Patient, who responded to liver therapy: was living 6.5 yr postoperatively
122	—	—	44.0	765	Patient, who responded to oral folic acid therapy: was living 5 yr postoperatively
118	37.9	—	34.2	687	No bone-marrow biopsy: slight response to prolonged folic acid therapy; patient living 5.5 yr postoperatively
—	—	—	—	50	Blood smear showed macrocytosis, anisocytosis and tailed cells, no bone marrow biopsy: patient, who responded to liver therapy: living 3.5 yr postoperatively
115	40.9	—	14.7	22	Blood smear showed macrocytosis: bone marrow showed megaloblastic picture: patient, who responded to oral folic acid therapy: living 9 yr postoperatively
—	—	—	—	42	Blood smear similar to that in pernicious anemia, but no nucleated red cells seen; liver therapy: patient probably that referred to by Duggan <sup>14</sup> as having died of pernicious anemia 11 yr postoperatively
—	—	—	—	—	No response to liver until administration of iron intravenously: patient living 8 yr postoperatively
—	—	—	—	—	Blood picture stated to reveal "macrocytic anemia"; patient responded to liver therapy but died of metastasis 3.5 yr postoperatively
—	—	—	—	—	Blood picture stated to reveal "profound anemia" (no blood count given); patient improved but relapsed, dying 3.7 yr postoperatively; no metastasis found at autopsy (incomplete study)
—	—	—	—	—	Macrocytic anemia: stated to have developed while patient was on prophylactic liver therapy: patient died of metastasis 4 yr postoperatively

striking but can partly be attributed to differences in fat intake and in subject material. In some cases, for example, the patients were studied early in the postoperative period before readjustment of gastrointestinal function was complete, in others, the patients subsequently died of recurrent carcinoma and the result that the effects of total gastrectomy and of the recurrent disease are hard to separate. The report of Heilmann,<sup>41</sup> often credited with describing a fat loss of 52 to 74 per cent, contains equivocal

lost is not large, but on high-fat diets, a considerable excretion of fecal fat may take place. The careful studies of Wollaeger et al.<sup>42</sup> indicate that fat absorption is similarly affected after partial gastrectomy.

The absorption of fat-like substances was further studied by means of the vitamin A tolerance test, 300,000 units being given by mouth. The results indicate that the blood in Cases 1 and 3 achieved a normal increase of vitamin A but that the tolerance curve in Case 2 was quite flat (Fig. 3). A remarkable



feature is the delayed absorption of the vitamin that appears to take place in all these cases. When vitamin A is injected into the jejunum of a normal person, the blood level is sharply elevated two hours after the injection.<sup>46</sup> The two-hour to three-hour levels of vitamin A in the gastrectomy cases, contrary to all expectations, were lower than corresponding levels obtained in normal persons taking the test dose by mouth. Two possible explanations are offered for the delayed absorption of vitamin A: the test dose, which is small in volume, is retained in the jejunal reservoirs until the patient is allowed

ture show little variation from normal. The largest nitrogen loss, 4.8 gm, was reported by Bull,<sup>41</sup> whose patient was studied three and a half months after operation and was given a high-fat diet.

It has been postulated that the secretion of pancreatic enzymes is greatly reduced after removal of the stomach.<sup>47</sup> Deficient pancreatic secretion may result either because the vagi are sectioned at operation or because the duodenal mucosa does not elaborate secretin normally if acid chyme fails to enter the duodenum. Pancreatic-enzyme studies in our cases, however, yielded essentially normal figures



A



B

FIGURE 1 *Dilatation of Jejunal Segment at Esophagojejunal Anastomosis*  
A demonstrates puddling of the barium meal in Case 1, and B that in Case 2

to eat and drink (after the three-hour sample), and pancreatic and biliary secretions, which facilitate the absorption of vitamin A<sup>46</sup> and which enter the bowel considerably above the esophagojejunal anastomosis, mix with the test dose only after considerable delay.

Judging from the prothrombin times (Table 3), the absorption of fat-soluble vitamin K is adequate. The normal serum levels of calcium and phosphorus also indicate that at least some vitamin D is being absorbed. Roentgenograms of the spine and pelvis revealed normal bone studies in 2 cases. In Case 1 considerable osteoporosis was noted, but no more than was evident before operation.

A normal person on an average diet excretes between 1 and 2 gm of nitrogen a day.<sup>49</sup> As Table 2 indicates, our cases and those reported in the litera-

except in Case 2, in which a partial pancreatectomy had been performed (Table 4).

Standard methods for collecting pancreatic secretions from the duodenum could not be carried out because of the operative procedure. Furthermore, it was considered desirable to determine the response of the pancreas to food intake after total gastrectomy rather than the response to Mecholyl or secretin. Accordingly, an egg-nog of standard composition was given to each patient after a collecting tube had been placed in the jejunum under fluoroscopic control. Half an hour later, constant suction was applied, and intestinal chyme collected in an iced container for one hour. The aspirated material was relatively free of egg-nog.

None of the patients had symptoms referable to biliary-tract disease. An oral Graham-Cole test in

Case 1 did not demonstrate any gall-bladder shadow. The other patients received the dye intravenously, and a normal filling of the viscus resulted in both

reasons absorption from the dilated small bowel is often subnormal, and dilatation of jejunal segments not only may delay fat absorption by the pooling

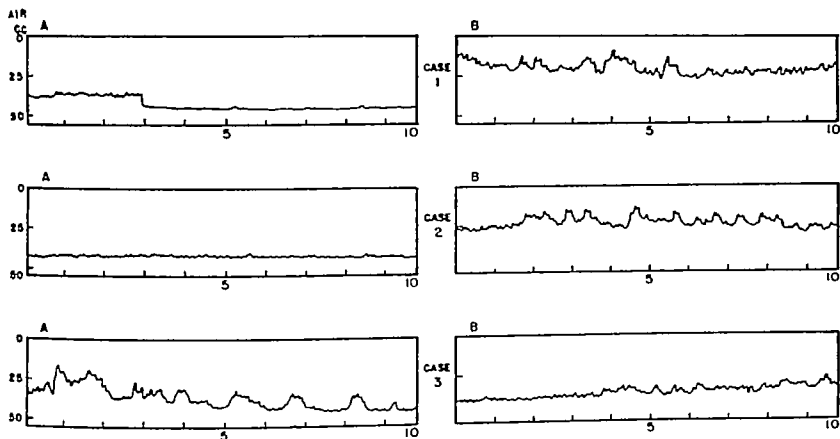


FIGURE 2. Balloon kymographic tracings of jejunal motility in Cases 1, 2 and 3

Tracing A was taken just below the esophageal anastomosis; tracing B refers to the lower jejunum. The vertical calibrations refer to air in the balloon, and the horizontal markings to time in minutes.

cases, administration of a fat meal produced normal emptying of the gall bladder.

Glucose-tolerance curves obtained after the 3 subjects had ingested 50 gm of glucose in 200 cc of water are presented in Figure 4. The early hyperglycemia that occurs in patients with extensive gastrectomies because a large quantity of hypertonic glucose solution rapidly enters the small intestine is well demonstrated and apparently is not affected by the presence of jejunal reservoirs. After the initial rise in blood sugar, a hypoglycemia attributed to excessively stimulated glucose removal mechanisms has been found in some of these patients,<sup>47, 48</sup> but such a response was not observed in our subjects. As a matter of fact, Case 2 exhibited a continuing hyperglycemia of the diabetic type, possibly related to the partial pancreatectomy that had been performed.

Significant impairment of fat absorption was demonstrated only in Case 2, but the deficiency of pancreatic enzymes in this patient suggests that the partial pancreatectomy was at least a contributing factor in the pathogenesis of the steatorrhea. In general, our studies indicated that such loss of fecal fat as may occur after total gastrectomy is not due to deranged function of the biliary tract or pancreas. By analogy to the delayed absorption of vitamin A, however, it is possible that the absorption of fats is impaired by mechanical disorders, for the following

of ingested food but also may decrease fat absorption by curtailing the length of normally functioning small intestine, and if jejunal pooling is minimal or

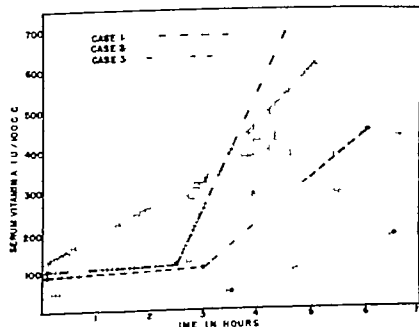


FIGURE 3. Vitamin A Tolerance Curves following Oral Ingestion of 300,000 International Units

The shaded area represents the normal range

is counteracted by the ingestion of a large meal, fats may be propelled for some distance down the intestine before pancreatic and biliary secretions

"catch up" with the meal. Under such conditions, fat absorption may be impaired because a relatively short stretch of small bowel is exposed to properly digested fats. In this connection, the pancreatic-function studies indicated that the jejunal reservoirs were practically free of egg-nog half an hour after its

hematologic findings in the other case were normal, but the patient had received liver prophylactically after operation. This incidence of macrocytic anemia prompted a renewed inquiry into the much debated question whether total gastrectomy predisposes toward a pernicious-anemia type of blood

TABLE 2 *Excretion of Fat and Nitrogen in Stools*

SOURCE OF DATA	YEAR OF REPORT	DIAGNOSIS	AGE OF PATIENT	SEX	INTERVAL BETWEEN OPERATION AND STUDY	INTAKE			FAT LOSS IN STOOL			PROTEIN LOST AS NITROGEN
						CARBO-HYDRATE	PROTEIN	FAT	PER DAY	PER-CENTAGE OF INTAKE	PER-CENTAGE DRY WEIGHT OF FECES	PER DAY
			yr		gm	gm	gm	gm				gm
Present report (Case 1)	1947	Carcinoma	58	F	10 yr	—	—	40-60	8 0	—	37 4	0 9
Present report (Case 2)	1947	Carcinoma	49	M	5 yr	—	—	40-60	14 5	—	35 0	2 2
Present report (Case 3)	1947	Ulcer	41	M	3 yr	—	—	40-60	7 8	—	19 1	2 6
Breitenbach <sup>14</sup>	1929	Ulcer	41	M	6 5 yr	165	138	135	8 1	6 0	—	0 9
Breitenbach <sup>14</sup>	1929	Carcinoma	51	F	5 wk.	126	91	116	8 2	7 1	—	0 6
Breitenbach <sup>14</sup>	1929	Carcinoma	—	—	3 mo	—*	—*	—*	—	7 0	—	—
Bull and Stang <sup>14</sup>	1934	Carcinoma	40	M	14 wk.	243	95	137	41 3	30 1	—	4 8
Bürger and Konjetzny <sup>15</sup>	1929	Carcinoma	49	F	3 wk.	96	34	86	10 2	11 9	—	0 4
Butler <sup>14</sup>	1927	Ulcer	42	M	5 mo	—†	—†	—†	—	—	38 0	—
Farris et al <sup>17</sup>	1943	Neuro fibroma	40	F	4 yr	245	67	89	1 5	1 7	7 3	0 8
Flint <sup>18</sup>	1928	Carcinoma	44	M	5 mo	—‡	—‡	—‡	—	—	40 7	—
Hofmann <sup>18</sup>	1898	Carcinoma	56	F	5 5 mo	185	93	84	4 6	5 5	—	—
Wróblewski <sup>18</sup>	1898	Carcinoma	56	F	1 mo	—	—	—	13 3	—	37 6	—
Kobelt <sup>19</sup>	1922	Carcinoma	45	F	1 mo	—	72	33	7 6	—	—	2 0
Longmire <sup>10</sup> 41	1947	Carcinoma	57	M	23 mo	—	—	77	30 8	40 2	41 3	—
Longmire <sup>10</sup> 41	1947	Carcinoma	53	M	29 mo	—	—	77	23 1	30 2	31 1	—
Longmire <sup>10</sup> 41	1947	Carcinoma	58	F	22 mo	—	—	77	7 2	9 4	25 2	—
Longmire <sup>10</sup> 41	1947	Carcinoma	62	M	24 mo	—	—	77	7 8	10 2	18 5	—
Rekers et al <sup>42</sup>	1943	Carcinoma	42	F	1 1 yr	—	25	50	12 0	24 0	—	1 0
Rekers et al <sup>42</sup>	1943	Carcinoma	55	M	4 mo	—	77	70	11 0	16 0	—	1 3
Rekers et al <sup>42</sup>	1943	Carcinoma	59	M	Over 1 yr	—	62	40	23 0	57 0	—	2 2
Troell et al <sup>44</sup>	1927	Carcinoma	47	M	5 wk.	304	118	182	34 4	18 9	—	3 1

\*Not stated — probably same amount as that in second Breitenbach case.

†Stated as "full diet."

‡Stated as "ordinary diet."

ingestion, but that at that time considerable quantities of relatively pure bile and pancreatic juice had collected in the dilated bowel loops.

Speculation concerning the ultimate effects of vagotomy on biliary, pancreatic and intestinal function has recently been rife. Since complete vagotomy is almost always performed during total gastrectomy,

picture. On theoretical grounds, it should, for Castle<sup>54, 55</sup> has shown that in man, as opposed to some animals,<sup>56</sup> the stomach is the only source of the intrinsic antianemic factor. Clinical experience, however, suggests that total gastrectomy in man is not followed by a macrocytic hyperchromic anemia, although an iron-deficiency anemia occasionally

TABLE 3 *Pertinent Data in 3 Cases after Total Gastrectomy*

CASE No	SERUM CALCIUM	SERUM PHOSPHORUS	SERUM CHOLESTEROL	TOTAL PROTEIN	SERUM ALBUMIN	SERUM GLOBULIN	ALBUMIN-GLOBULIN RATIO	PROTHROMBIN TIME	BROM-SULFALAN REMOVAL CONSTANT <sup>44</sup>
	mg / 100 cc	mg / 100 cc	mg / 100 cc	gm / 100 cc	gm / 100 cc	gm / 100 cc		PATIENT CONTROL	%
1	9.94	3.62	165	6.49	4.13	2.36	1.75 : 1.0	23.7 sec 23.0 sec	11.45
2	8.74	3.52	177	5.85	3.22	2.63	1.23 : 1.0	22.2 sec 22.5 sec	7.80
3	10.20	3.34	173	6.60	3.98	2.62	1.52 : 1.0	23.8 sec 23.7 sec	15.20

it is of interest that our patients did not manifest the dire results that have been predicted as sequelae to section of the vagus nerves.

#### MACROCYTIC ANEMIA

As shown in Table 1, 2 patients developed a macrocytic, hyperchromic anemia two and five years, respectively, after total gastrectomy. The

occurs. Thus, Pack and McNeer<sup>57</sup> state that a macrocytic anemia is rare after total gastrectomy, and that when it is found, it is seldom hyperchromic and usually does not respond to adequate liver therapy.

The blood findings in our patients suggested the hypothesis, which had already been advanced by others,<sup>58</sup> that patients with total gastrectomy de-

velop macrocytosis and hyperchromia provided they live long enough after the operation. For this reason, we have collected from the literature and by personal correspondence as many cases of three-year survival after total gastrectomy as possible, and have attempted to ascertain the incidence of macrocytic anemia in this group 25-31, 37-39, 46, 51, 52-54. Some cases previously cited as three-year survivals

died one year postoperatively of acute small-bowel obstruction. At autopsy no evidence was found of recurrence of carcinoma. This case has been omitted from Table 1, which is limited to three-year survivals.

The 29 patients who apparently did not develop a macrocytic anemia include 10 who definitely had not received prophylactic liver therapy. No definite

TABLE 4 Enzyme Analysis of Jejunal Chyme

CASE NO.	AMYLASE*		LIPASE†		TRYPSIN‡	
	VOL. IN 1 HR. cc	units/cc	TOTAL units in 2 hr	units/cc	TOTAL units in 2 hr	units/cc
1	80 0	11 0	880 0	61 2	4 896 0	200 0
2	107 0	2 2	215 4	16 1	1 723 0	7 2
3	48 5	10 3	499 5	49 2	2,386 2	200 0

\*Determined by method of Lagerlöf 44

†Determined by method of Crandall and Cherry 46

‡Determined by method of Andersen and Early 44 slightly modified.

after total gastrectomy are not included because removal of the stomach was not total. For similar reasons, or because of insufficient data, certain cases of alleged macrocytic anemia after total gastrectomy are excluded 25-31.

After exclusion of patients definitely known to have received prophylactic treatment with liver, 46

information is available whether or not liver was given in the other 19 cases (Table 5).

In the 12 cases with macrocytosis and hyperchromia, a pathological diagnosis of ulcer or gastritis was made in half, whereas none of those with malignant lesions had any evidence of recurrence. Generally speaking, these patients had a satisfactory

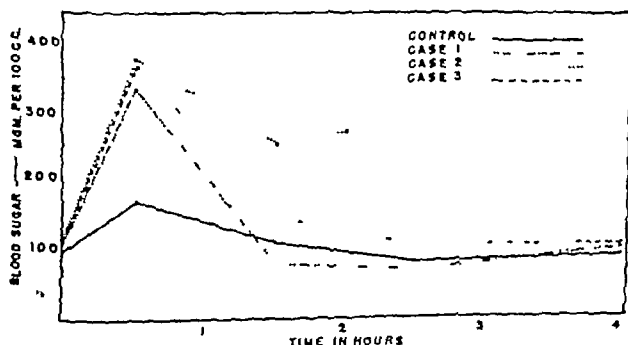


FIGURE 4 Oral Glucose Tolerance Curve following Administration of 50 gm. of Glucose Dissolved in 200 cc of Water

cases remain. Of these, 12 appear to have had blood findings resembling those of pernicious anemia, and 5 others had anemias of doubtful nature.

Another case of macrocytosis and hyperchromia — red-cell count of 3,810,000, hemoglobin of 95 per cent (Sahli), mean red-cell diameter of 8.8 microns and nucleated red cells found on smear — is reported by Ungley 52. This blood picture developed five months after total gastrectomy, but the patient

surgical result, and it seems probable that their diet was adequate. It is noteworthy that 3 cases showed a definite reduction in the red-cell count, with an increase in the mean corpuscular volume, but relatively little decrease in hemoglobin. It is possible that this is the earlier stage of this type of anemia.

Macrocytic anemias seldom occurred less than two years after operation. This finding was also

noted in the studies of similar anemias occurring after less radical gastric resection<sup>94, 95</sup> Why so long a time is required to develop this blood picture is unknown Schwartz and Legere<sup>96</sup> recently reported that self-induced relapses in 54 patients who had

have been administered indiscriminately, and special studies like reticulocyte counts and bone-marrow examinations have been few Only if macrocytic anemias that follow total gastrectomy are carefully investigated by the methods used by Meyer et al<sup>3</sup>

TABLE 5 *Patients Surviving Total Gastrectomy for Three or More Years without Developing a Macrocytic Anemia*

SURGEON	DATE OF OPERATION	AGE	SEX	DIAGNOSIS	REMARKS
Patients not given liver therapy					
Berg	1931	51	M	Carcinoma	Patient died 3 yr after operation
(Rosenthal-Abel <sup>99</sup> )					
Brigham <sup>27</sup>	1898	66	F	Carcinoma	Patient well 8 yr after operation
Brun	1916	45	F	Carcinoma	Patient died of chronic nephritis 4 yr after operation
(Kobelt <sup>29</sup> )					
Butler	1926	42	M	Ulcer	Patient well 5 yr after operation, with normal blood picture
(Hurst <sup>30</sup> )					
Diaz	1941	54	M	Carcinoma	Patient well until sudden death from cardiac failure 4 yr after operation
(Milanes <sup>42</sup> )					
von Haberer <sup>44</sup>	1920	56	M	Ulcer	Patient died of tuberculosis 6 yr after operation
von Herczel <sup>45</sup>	1901	42	F	Carcinoma	Patient well 5 yr after operation
MacDonald <sup>46</sup>	1898	38	M	Carcinoma	Patient well 7 yr after operation
Ransom	1938	40	F	Neuro-fibroma	Patient well 8½ yr after operation
(Farris et al <sup>47</sup> )					
Wrede <sup>47</sup>	1919	36	M	Carcinoma	Patient well 4 yr after operation
Definite information on liver therapy not available*					
d'Allaines <sup>25</sup>	1941	44	M	Carcinoma	Patient well 3½ yr after operation
Allen <sup>48</sup>	—	—	M	Carcinoma	Patient died 4½ yr after operation
Joll <sup>70</sup>	1932	45	M	Carcinoma	Patient died 3 yr after operation
Joll <sup>70</sup>	1938	42	F	Carcinoma	Patient died 3½ yr after operation
Lahey Clinic operators	1938	50	M	Carcinoma	Patient died 4¼ yr after operation
(Smith <sup>44</sup> )	1940	64	M	Carcinoma	Patient well 5½ yr after operation
	1941	51	F	Lymphoma	Patient well 4½ yr after operation
	1941	60	F	Carcinoma	Patient failing 4 yr after operation
	1941	62	F	Carcinoma	Patient died 3 yr after operation
	1942	64	F	Carcinoma	Patient well 3¼ yr after operation
	1942	51	M	Lympho-sarcoma	Patient well 3½ yr after operation
	1942	57	M	Carcinoma	Patient died 3½ yr after operation
	1943	56	F	Chronic gastritis	Patient well 3 yr after operation
Mayo Clinic operators					
(Waugh and Fahlund <sup>72</sup> )	—	—	—	"Malignancy"	Patient alive over 3 yr after operation
				"Malignancy"	Patient alive over 3 yr after operation
				Benign tumor	Patient alive over 6 yr after operation
Roeder <sup>73, 74</sup>	1932	50	M	Ulcer	Patient well until sudden death from cardiac failure 6 yr after operation
Seo <sup>75</sup>	—	—	—	Carcinoma	Patient living 3 yr after operation
Weese <sup>76</sup>	—	—	—	Carcinoma	Patient died 3½ yr after operation
Patients given liver therapy prophylactically					
Allen <sup>48, 49</sup>	1939	39	F	Carcinoma	Patient died 4½ yr after operation
Lahey Clinic operators	1929	36	F	Carcinoma	Patient died 3¼ yr after operation
(Clute <sup>77, 78</sup> )					
Lahey Clinic operators	1937	27	F	Leiomyo-sarcoma	Patient well 8½ yr after operation
(Smith <sup>44</sup> )					
Morton <sup>79, 80</sup>	1939	48	F	Carcinoma	Patient well 8 yr after operation
Morton <sup>79, 80</sup>	1940	38	M	Carcinoma	Patient well 7 yr after operation
Ransom <sup>41</sup>	1938	52	M	Carcinoma	Patient had pernicious anemia preoperatively, well 8 yr after operation
Smithwick <sup>1</sup>	1936	58	F	Carcinoma	Patient well 10½ yr after operation

\*Most of the patients operated on at the Lahey Clinic probably received liver<sup>44</sup>

been treated with liver occurred two to thirty-eight months after cessation of therapy for pernicious anemia They stress the fact that relapse is a highly singular phenomenon that is unpredictable in any given case This individual variation is also seen in the macrocytic anemias after total gastrectomy

The evidence appears to support the statement that an anemia morphologically similar to Addisonian pernicious anemia will develop after total gastrectomy if the patient survives long enough Whether the anemia is truly Addisonian, or whether it is another form of macrocytic anemia requires further study In the past, most patients developing macrocytic anemia after total gastrectomy have been incompletely studied, for the effects of dietary deficiency have not been excluded, liver and iron

can their relation to Addisonian pernicious anemia be clarified

### SURVIVAL

A review of the literature to determine the incidence of anemia in patients surviving total gastrectomy for more than three years uncovered so many inconsistencies and forgotten cases that a note on the period of survival following total gastrectomy seems indicated

Until recently, the patient of Zikoff<sup>97</sup> was considered the longest survival after total gastrectomy for carcinoma, since Finney and Rienhoff<sup>98</sup> reported her alive four years and eight months after operation Zikoff's article, however, is an early post-operative report, which does not contain any in-

formation concerning subsequent survival. Attention is directed to a much overlooked reference, the Hunterian lecture of 1906, by H. J. Paterson.<sup>9</sup> In this monograph, he quotes a personal communication from MacDonald, of San Francisco, to the effect that the patients of Brooks Brigham and of MacDonald were alive and well eight and seven years after their operations, which, incidentally, were the second and third successful total gastrectomies reported in the literature. One of the patients studied by us is alive and well ten and a half years post-operatively, whereas the patient described by Poole and Foster<sup>9</sup> is still alive and well 20 years after the complete removal of the stomach for a nonmalignant condition.<sup>10</sup> These 2 cases appear to represent the longest known survivals after total gastrectomy for malignant and nonmalignant tumors respectively.

SUMMARY

Studies on 2 patients who had survived total gastrectomy ten and three years respectively and on 1 who had survived total gastrectomy, splenectomy and partial pancreatectomy five years revealed the clinical condition of the patients with total gastrectomy alone to be excellent. Considerable dilatation of the jejunum near the esophagojejunal anastomosis was demonstrated by roentgenologic and kymographic methods in 1 case. In both cases, pancreatic enzymes were normal, and fat absorption on a low-fat intake was not significantly impaired. Vitamin A tolerance curves showed an apparently delayed but otherwise normal absorption of the vitamin. Glucose-tolerance tests disclosed an early and marked, but transient, hyperglycemia.

The patient with total gastrectomy, splenectomy and partial pancreatectomy experienced difficulty in maintaining weight. Dilatation of the jejunum was present. Pancreatic enzymes were deficient, fat absorption impaired, and the vitamin A tolerance curve flat. The glucose-tolerance curve showed a hyperglycemia, which was sustained.

Blood studies demonstrated that 2 of the 3 patients developed a macrocytic, hyperchromic anemia two and five years respectively after operation. The other had received prophylactic liver treatment. A review of the literature revealed a high incidence of macrocytic, hyperchromic anemia in patients surviving total gastrectomy for three or more years.

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## A REVIEW OF SOME RECENTLY DEFINED VIRUS DISEASES\*

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**D**URING the decade 1920-1930, when I first began the study of infectious agents, it was more or less generally agreed that the era of etiologic discovery, if not definitely ended, was at least in its final stage. The efforts of bacteriologists in the future were to be directed to the more intensive study of the known pathogenic organisms—the number of which would not be materially increased—with a view to defining more precisely their metabolism, their chemistry, the immune reactions that they elicited and the means by which their attack might be prevented or withstood. However, we failed to visualize that rapid extension of its boundaries that was so soon to come! Since 1930 not only have the causative agents of such old and important diseases as yellow fever, influenza and mumps been determined but also the etiology of a large group of other infectious maladies, many of which had been clinically unrecognized, has been established. If the diseases of the lower animals that have been described during the same period are included the number of additions to this area of pathology becomes impressive indeed. To emphasize the fact that the age of etiologic discovery is far from ended, the following fairly complete list of diseases in man is given for which, within the period from 1940 to 1946, either conclusive or presumptive evidence of viral etiology has been presented: primary atypical pneumonia, Reimann's epidemic diarrhea epidemic keratoconjunctivitis, Colorado tick fever, Russian spring-summer encephalitis, equine encephalomyelitis (Venezuelan strain), infectious jaundice, homologous serum jaundice, Dodd-Buddingh stomatitis and diarrhea of infants (final establishment of etiology requires confirmatory experiments), epidemic diarrhea of the newborn (final establishment of etiology requires confirmatory experiments), Fort Bragg fever or pretibial fever, West Nile fever (Africa), and Semliki forest fever (Africa). Indeed, after this list was prepared, a new virus disease was reported by a group of workers in Tennessee.<sup>1</sup> An outbreak of epidemic meningoencephalitis accompanied by vesicular pharyngitis affected over 200 persons, and inoculation of filtrates of nasopharyngeal washings from certain patients into the embryonated egg resulted in the isolation of what is tentatively described as a virus differing from any of the known agents.

It is my purpose to discuss mainly from the etiologic standpoint the first three diseases listed above. Of these primary atypical pneumonia and epidemic diarrhea have been of common occurrence in these regions. Epidemic conjunctivitis has been recognized in New York and the surrounding areas, although it seems first to have been clearly described on the Pacific Coast. As knowledge of it becomes more widely disseminated it is probable that more and more cases will be recognized.

## PRIMARY ATYPICAL PNEUMONIA AND MINOR ACUTE UPPER RESPIRATORY ILLNESS

In a small number of patients with primary atypical pneumonia a fungous infection, the rickettsia of Q fever or the viruses of the psittacosis-ornithosis group have been shown to be involved.<sup>2</sup> But the determination of the nature of the agent responsible for the majority of cases has presented a baffling problem to investigators ever since this condition was recognized as a clinical entity in the years just preceding the war. At that time intensive efforts to reveal a virus in the blood, sputum and nasopharyngeal washings were made. These materials were obtained from patients studied clinically by Bock<sup>3</sup> and by Murray,<sup>4</sup> who were among the first to describe the disease in this area. My results, like those of many others reported at that time and subsequently, were entirely negative. A few investigators, however, claimed to have isolated a virus. Thus, Weir and Horsfall<sup>5</sup> produced a nonbacterial pneumonia in the mongoose and Eaton and his co-workers<sup>6</sup> described the propagation of a filterable agent in cotton rats and the embryonated egg. These observations have not as yet been confirmed by other workers.

By 1944 it was therefore obvious to most investigators that the agent of this disease was closely adapted to the human host—perhaps so closely adapted that it could not be established in any other animal species. Accordingly, the Commission on Respiratory Diseases<sup>7</sup> located during the war at Fort Bragg, North Carolina, undertook experiments in human volunteers with the objective of proving whether the agent was transmissible and filterable. The results of these elaborate and costly experiments leave no reasonable doubt, I believe, that atypical pneumonia in which none of the known bacterial, fungal, viral or rickettsial agents can be demonstrated is due to a filterable virus. In all, three experiments were carried out in which pooled sputums and nasal washings from patients with character-

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tic cases of atypical pneumonia were inoculated by the respiratory route into human volunteers. In the last two, the subjects were divided into three groups, one of which received material passed through a bacteria-retaining filter, another unfiltered washings and a third unfiltered material that had been autoclaved. A condition compatible with atypical pneumonia was produced in some of the subjects inoculated in all three experiments. For example, in the last experiment, the typical disease was caused in 3 of the 12 men who received filtrate and in 3 of 12 others who were given the unfiltered material. The incubation period following inoculation with filtered material was approximately fourteen days, and that with unfiltered material approximately seven days. None of the 18 men who received autoclaved material (the control group) developed the disease. Since in this last experiment in particular every precaution was taken to eliminate the possibility of spontaneous infection, the results may be accepted as indicating that atypical pneumonia is due to a nonbacterial, filter-passing agent.

It is of great interest, regarding the current epidemiologic views concerning atypical pneumonia, that 10 of the 24 men who received the unautoclaved material developed minor upper respiratory illness of an undifferentiated type, without signs of lung involvement, since it has been the opinion of clinical students of the disease that during epidemics many persons become infected with the virus who do not develop pneumonia but only mild upper respiratory symptoms. It should be pointed out, however, that whereas these results strongly suggest that the virus of atypical pneumonia frequently gives rise to a non-pneumonic type of infection, they do not prove that the same agent is responsible for both diseases, since the possibility of the presence of two viruses in the inoculum was not ruled out.

The Commission also concerned itself with the relation between two other frequent clinical types of acute respiratory illness and their etiologies. Thus, in additional experiments with 42 volunteers,<sup>8</sup> they inoculated material obtained from a person with symptoms mainly of coryza — that is, those of the common cold and with minimal signs of pharyngeal inflammation. Another group was inoculated with materials from a patient with an infection distinguished from the common cold principally by sore throat and little nasal involvement. The results indicated clearly that both these clinical types of infection could be experimentally transmitted to human beings by means of filtrates of throat washings. The most interesting finding, perhaps, was the difference in the incubation period of the two types of experimentally induced disease. The coryzal syndrome had an incubation period of one or two days — an observation in agreement with earlier work on the common cold by Dochez and others. In contrast, the disease characterized chiefly by inflammation of the pharynx had an incubation period of

five or six days. It will be noted that both these periods of incubation were shorter than that of the experimental atypical pneumonia. Worthy of emphasis, too, is the finding that no immunity apparently resulted from the experimental coryzal infection, since reinoculation within three weeks with active material from patients who had recovered again induced the disease. On the other hand, the pharyngitis virus produced a specifically increased resistance following reinoculation. Neither the common cold nor the pharyngitic syndrome induced immunity against experimental inoculation of material containing the virus of atypical pneumonia. The participation of hemolytic streptococci or influenza virus in either type of infection was satisfactorily eliminated as a possibility.

In concluding this brief discussion of nonbacterial, acute respiratory disease, exclusive of influenza, it can be stated that although knowledge of these conditions is still distressingly chaotic, definite progress has been made toward an ultimate etiologic classification. Certainly, one can be reasonably certain that the nature of the etiologic agent in primary atypical pneumonia has been defined. The infection may be recognized not only by x-ray findings but also, in many cases, through the application of the test for cold agglutinins<sup>9</sup> or the Thomas agglutination test employing the indifferent streptococcus MG<sup>10</sup>. This information on etiology and on diagnostic aids indicates how much progress has been made in a very difficult problem within a short time. When suitable laboratory facilities are available, full advantage should be taken of them by physicians in the diagnosis of suspected cases of this disease.

#### REIMANN'S EPIDEMIC DIARRHEA

The occurrence of outbreaks of diarrheal disease, usually mild in character and acute in nature and lasting ordinarily twenty-four or forty-eight hours, has long been observed and has been reported in the medical literature from many parts of the world. The common enteric bacterial pathogens have often been conspicuously absent in such outbreaks, which are prone to occur in institutions such as schools, barracks and hospitals. The mild character of these epidemic gastrointestinal disturbances has been mainly responsible for the lack of efforts toward the elucidation of the responsible agent. Clearly infectious in their behavior, such epidemics do not appear to be occasioned by contaminated food, water or milk. This type of illness in adults, interesting enough in itself, has of late attained additional significance because of possible relations to the cause of the highly fatal diarrhea of the newborn that Clifford<sup>11</sup> has discussed. Accordingly, it seems pertinent to emphasize the studies in which Reimann and his associates<sup>12</sup> recently described and investigated an outbreak of epidemic diarrhea among medical students in Philadelphia. This epidemic was similar in all respects to many others that have

been recorded. In general, such outbreaks have had the following characteristics:

They tend to occur in the autumn but there are no strictly seasonal limitations.

Children and young adults appear to be particularly susceptible, but no age group is resistant.

The morbidity is high, ranging from 15 to 100 per cent.

Usually, there is no mortality.

The symptoms, which follow an incubation period of about two days in most cases, consist of anorexia, nausea, vomiting, diarrhea, dizziness, aching and abdominal discomfort or cramps. Not all these manifestations, of course, are always noted in the same person.

Fever is exceptional.

Occasionally, there are concomitant signs of mild upper respiratory disease, a fact that has sometimes been responsible for the diagnosis of so-called "intestinal flu." I have had occasion to follow the investigation of two outbreaks of epidemic diarrhea in state institutions during the last few months. In every respect they conformed in epidemiologic pattern and clinical picture to Reimann's outbreak, except that in a few cases of aged and sick patients the disease seemed to be a contributing factor to their deaths.

Because of the failure to incriminate any of the usual vehicles of transmission of enteric diseases of known etiology, Reimann and his associates<sup>13</sup> investigated experimentally in volunteers the hypothesis that this disease was communicable via the respiratory route. Thirty-two healthy young adults were permitted to inhale nebulized garglings obtained from patients with the typical symptomatology, after the material had been filtered to remove bacteria. Similarly, stool filtrates from patients with acute cases were administered in the form of a fine spray to 21 other volunteers. In each group approximately half the subjects developed symptoms of the disease. In most cases those who became ill did so one to four days after inoculation, thus giving evidence of the probable duration of the incubation period. Unfortunately, these experiments were carried out at a time when the epidemic, although definitely on the wane among the general student body, was still active, and since rigorous precautions for isolation were not possible, the results might be questioned. However, when one considers that the incidence of disease among the student body was only 9 per cent, as contrasted with 53 per cent among the inoculated subjects, there can be little doubt that in the majority of cases the disease had been induced by means of bacteria-free filtrate administered by the respiratory route. That the natural mode of transmission is probably by this route is supported by the fact that no symptoms developed

in a number of volunteers who swallowed capsules containing filtrates of garglings or stools.

As yet there has been little work in attempting to isolate a virus in the laboratory from epidemic diarrhea. Reimann and his associates<sup>14</sup> failed to infect young mice and the chorioallantoic membrane of the embryonated egg. Experiments in our own laboratory are now being carried on with the purpose of investigating this problem more intensively. To my mind these observations of Reimann are of much significance not only because they seem to represent the best evidence so far presented that a virus can cause a characteristic enteric disease but also, taken with other recent information, because they strongly suggest that a whole group of similar agents are involved in various clinical types of acute gastrointestinal disorder.

#### EPIDEMIC KERATOCONJUNCTIVITIS

Epidemic keratoconjunctivitis is a disease that has long been known but in which the etiology has been obscure. First described by Fuchs in 1889, epidemics have subsequently occurred throughout the world. Not until 1941, however, was the disease reported in the United States, where it emerged as an epidemic in shipyards on the Pacific Coast.<sup>15</sup> Since that time cases have been described elsewhere in this country. In the East, outbreaks have occurred in the area around New York City,<sup>16</sup> in Connecticut and in western Massachusetts. It tends to be epidemic in industrial plants but may occur sporadically, and has been shown to be spread in physicians' offices and ophthalmic dispensaries where proper aseptic technics have not been employed.

The disease is characterized by nonpurulent inflammation of the conjunctivas, preauricular lymphadenitis and superficial punctate corneal opacities. There may be accompanying symptoms of headache, malaise and slight fever. The incubation period is unknown in the natural disease, which lasts from two to four weeks or longer. Recovery is usually complete, although in a small percentage of patients keratitis with impairment of vision may persist. Although earlier experimental work pointed to a filterable virus, it was not until the work of Sanders and Alexander in 1942<sup>17</sup> that the etiology was finally established. With conjunctival scrapings of 2 patients these investigators obtained a mild encephalitic disease following the intracerebral inoculation of white mice. More decisive results were obtained after the cultivation of mouse brain containing the virus in tissue culture with subsequent mouse passages. This somewhat unconventional procedure appeared to enhance the virulence of the virus for mice so that intracerebral inoculation was regularly followed by death. But subsequently, in 1945 Maumenee and his associates<sup>18</sup> isolated a strain of virus that was from the outset of high virulence for mice since it regularly killed these animals within three to five days after intracerebral inoculation.

The mouse-adapted strain of this virus was then cultivated in the embryonated egg by Calkins and Bond<sup>19</sup>

The relation of the virus to the human disease was demonstrated in two ways by Sanders and Alexander<sup>17</sup> instillation of a suspension of mouse brain into the conjunctival sac of a volunteer resulted in a modified but typical attack of keratoconjunctivitis, and patients recovering from the disease were shown to develop antibodies that specifically neutralized the virus. Such antibodies were not found earlier in the disease or in a number of normal human subjects. On the other hand, the pathogenicity of the virus for mice was not neutralized by antibodies against lymphocytic choriomeningitis, Theiler's mouse poliomyelitis and serums from patients suffering from nonspecific conjunctivitis or keratitis. These workers also found the virus to be distinct from the herpes virus on the basis of virus-neutralization tests with appropriate antisera. Maumenee and his associates,<sup>18</sup> however, discerned an antigenic similarity between the virus of keratoconjunctivitis and that of herpes. In spite of this discrepancy in the findings of the two groups of workers the viruses are quite distinct, since animals actively immunized against herpes virus have been shown to be resistant to herpes but not to the epidemic keratoconjunctivitis virus. Moreover, significant differences in the size of the infective particles of the two viruses have been determined. The data indicating that the viruses can be distinguished from each other in the laboratory are important because the herpes virus, as is well known, can cause a conjunctivitis with involvement of the cornea that could be confused with that due to the virus of epidemic keratoconjunctivitis, although certain clinical features of herpetic keratoconjunctivitis are characteristic, such as the dendritic processes of the lesion. The lack of epidemic spread of herpetic conjunctivitis also represents an important differential feature. The clinical similarity is close enough, however, so that recourse should be had to a suitably equipped laboratory if a final etiologic diagnosis is to be made. So far as I know, epidemic keratoconjunctivitis has been a rare disease in Massachusetts, but the possibility exists that epidemics may occur at any time.

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Little or nothing has been said above regarding specific prevention or therapy, because there is as

yet little or nothing to say regarding these always pressing concerns. But with the greatly increased interest and activity in the realm of viruses, it is by no means impossible that in the not too distant future one talking about the various categories of diseases exemplified by the infections I have discussed may have a different story to tell.

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## MEDICAL CARE FOR THE PEOPLE OF MASSACHUSETTS THE CONTRIBUTION OF BLUE SHIELD\*

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THERE are now fifty-seven medical-care plans sponsored by medical societies and operating in thirty-three states. They cover approximately 4,500,000 persons. Fifty-five of these plans are nonprofit, the other two utilize the services of commercial insurance carriers. In the fifteen states that do not have plans in operation, nonprofit plans are being organized in seven, commercial plans are being organized in three, and preliminary discussions are under way in four. This leaves but one state in which nothing tangible is being accomplished.

Much of the credit for this remarkable picture must go to the Council on Medical Service of the American Medical Association, which since its creation in 1943 has not only prompted the establishment of plans in many areas but also given marked impetus to the medical-care-plan movement as a whole.

Although well able to carry on its promotional functions, the Council early realized that it was not in a position to cope with the technical aspects of development and co-ordination. Consequently, about a year ago, it sponsored a meeting of plan executives, out of which came an independent organization known as Associated Medical Care Plans. Between annual meetings of the members, the affairs of this association are directed by a nine-man commission that includes three representatives from the Council on Medical Service.

Although there is necessarily some overlapping of the interests and activities of the Council on Medical Service and the Commission of Associated Medical Care Plans, the Council is primarily concerned with promoting the establishment of plans and determining broad concepts of policy that should characterize the prepayment movement. The Commission, on the other hand, is primarily occupied with the day-to-day problems of plan organization and operation and with interplan relations.

Of the sixty-two nonprofit plans now in operation, or about to operate, forty-one are members of Associated Medical Care Plans, and it is expected that the remaining twenty-one will become members in the very near future. Although not specifically excluded, it is highly unlikely that any commercial plan will be admitted to membership.

With nearly 600,000 persons covered, Massachusetts Medical Service (Blue Shield) is the second

largest and one of the most successful medical-care plans in the nation. In retrospect, the primary reasons for these achievements are not hard to find and may be briefly summarized as follows:

The Board of Directors is made up of one third physicians and two thirds laymen. Lay representation is almost equally divided between the population segments broadly defined by the terms labor and management. In the conduct of a million-dollar enterprise, it is absolutely essential that provision be made for guidance by trained businessmen. Similarly, in any organization that deals directly with hundreds of thousands of persons it is essential that certain of their attitudes be constantly appraised by experts in such matters.

All rules and regulations pertaining to medical relation must be initiated by the physicians on the Board and approved by the Executive Committee of the Council of the Massachusetts Medical Society. It is now generally acknowledged that in any kind of medical-care program, determinations concerning medical matters must be delegated to the physicians involved.

Income limits, below which members are entitled to service benefits without additional charge, must be approved by the Council of the Massachusetts Medical Society. The level at which income limits are established is a direct measure of the willingness of the medical profession to assume a fundamental sociologic obligation on behalf of persons in the low and moderate income groups and therefore has a direct influence on sales resistance and the attitude of the public toward the profession. Consequently, it is of the utmost importance that these determinations be based on enlightened professional self-interest. When Massachusetts Medical Service was established, approximately 80 per cent of the wage-earning population of the Commonwealth was in the under-income category. With increased earnings during the war, this figure fell to 65 per cent, where it remained until recent action of the Council raised the limit for the family to \$3000 and thus restored the original relation, which, incidentally, is becoming recognized as standard for the nation.

Physician participation, initially in the neighborhood of 50 per cent, has steadily increased to its present level of more than 90 per cent. With payments for services by nonparticipating physi-

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cians within the Commonwealth virtually excluded, it is absolutely essential that a large percentage participate and that they be well distributed throughout the Commonwealth, otherwise the plan degenerates into a straight cash-indemnity arrangement

The administrative relation with Massachusetts Hospital Service, Incorporated (Blue Cross) has been eminently successful. Below the policy-making level there is practically no discernible distinction between the two organizations

As presently constituted, Massachusetts Medical Service (Blue Shield) provides benefits only for surgical and obstetric services rendered in the hospital. On June 1, 1947, this program will be extended to include benefits for medical (nonsurgical) services rendered in the hospital and for surgical and obstetric services rendered outside the hospital. Inclusion of benefits for medical (nonsurgical) services rendered outside the hospital is not anticipated in the immediate future because this type of coverage is financially hazardous unless undesirable coinsurance features are imposed or unless subscription rates are increased beyond the present point of public acceptance

Implementation of any program directly affecting the public is bound to arouse a crossfire of conflicting interests. Difficulties both predictable and unpredictable arise. Nevertheless, if such a program is to survive and prosper in a democracy, its difficulties must ultimately be resolved in the interest of the public

Many studies made during the past few years have indicated that the American people favor prepayment of the cost of medical and hospital care. Acknowledging this interest, the American Medical Association and its constituent societies are now committed to the principle of prepayment, with the reservation, however, that it be developed under voluntary auspices. With the imposition of this qualification, the medical profession assumed a tremendous obligation

To meet this obligation, medical societies have set up their own prepayment plans in thirty-one states. In two other states the societies have called upon commercial insurance carriers. The only point of distinction between the prepayment movement as it developed in Great Britain and on the Continent and as it is being developed here is that the

medical profession in the United States has sought to meet its own responsibility without the interposition of a third party imbued with interests foreign to the basic concepts that characterize medical practice. Should a wholesale tendency on the part of physicians to hand over their acknowledged responsibility to commercial carriers at any time develop, it is safe to predict that American medicine will quickly fall into the hands of the Government

Although it may be assumed that medical-care plans sponsored by medical societies will be in operation in all states in the near future, it would be fatal to assume that the obligation of the medical profession will thereby be resolved. To establish a medical-care plan is one thing, to keep it operating on a satisfactory basis is another

Up to the present, Massachusetts Medical Service (Blue Shield), which is one of the older plans, has encountered no serious problems, mainly because the number of plan patients that any given physician may see is not large. However, the picture is now rapidly changing. Present enrollment is in the neighborhood of 600,000 persons, and it seems safe to predict that by this time next year the figure will reach 1,000,000 or more. The result is that previously casual professional relations are becoming less casual as more and more physicians come to realize that by its very nature an expanding medical prepayment plan, while solving many problems, introduces new ones. From his own economic standpoint, for instance, it becomes increasingly incumbent upon the physician to establish a routine that will effectively identify plan patients and establish their income status. Similarly, from the standpoint of the plan patient, a routine of this sort must be developed if confusion and delay, with consequent ill feeling, are to be avoided

Fortunately, the vast majority of problems that arise lend themselves to reasonable solution. Nevertheless, they frequently require professional concessions, which must be made if the program is to accomplish its objectives and satisfy rational public demands. Massachusetts Medical Service (Blue Shield) is an organ of the Massachusetts Medical Society. Its board of directors is elected by the Executive Committee of the Council. Every physician has a direct voice in its affairs through his district professional service committee. Its problems are the problems of the profession, and its success or failure will largely be determined by professional attitudes now in the process of development

## REHABILITATION OF THE EMPLOYEE INJURED IN INDUSTRY\*

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IN THE life of the average workingman there is nothing more serious than the loss of his earning capacity. A serious injury with prolonged disability has far-reaching effects, not only on the man himself but also on his family. Plans for the purchase of a home and for education of his family are uppermost in the minds of most workingmen — plans that may have to be abandoned as a result of an industrial accident. It is only natural, therefore, that a person so injured should look to his doctor for the treatment that will restore him to his job in the best possible condition in the shortest possible time. It is clearly the physician's duty to give his very best from the minute of injury until the patient can return to work.

In the past few years progress in the treatment of traumatic lesions has come largely through the perfection of technique in the handling of the acute emergency. In this regard tremendous strides have been made. Most men who have kept abreast of the literature and who are aware of the modern methods of treatment can handle the acute emergency with competence. Treatment when the emergency is over, however, leaves much to be desired.

All physicians are more or less x-ray conscious and are apt to be most concerned with the roentgenographic appearance of the patient's lesion. However, we are likely to be entirely oblivious of the physiologic, pathologic and mental changes that may be developing in the patient. Failure to recognize such changes, produced by immobilization and enforced recumbency, may seriously delay the recovery of patients who have had efficient treatment in the emergency. Until these changes are recognized they cannot be prevented, and the patient's convalescence will be extended. Inadequate after-care is one of the great weaknesses of present-day surgery.

The first of the complications or changes that must be prevented is atrophy. When a patient is forced to remain in bed, all the tissues, particularly skeletal muscle, undergo atrophy. The second change is joint stiffness. The longer the period of recumbency, the more extensive atrophy and joint stiffness become. We have all seen patients too weak to sit up and too stiff to walk when their injuries have sufficiently healed to allow them to do so. This leads to further recumbency and the development of a vicious circle. Unfortunately this

condition is not uncommon and is a definite reflection on present-day treatment. General body and muscular tone can be maintained and joint stiffness prevented if patients perform simple exercises while in bed. There is usually no reason why such exercises cannot be performed in parts remote from the site of injury. The exercises not only benefit the patient physically but also help develop a feeling of well-being and, of utmost importance, help to bolster morale. Such exercises must not be left to the patient. The physician must see to it that these exercises are done, and done intelligently. By such means, the period of disability can be cut down and the patient's physical condition improved when he is ready to become ambulatory.

When it is necessary to splint a part, atrophy is much more rapid and extensive, and joint stiffness more likely to occur. Therefore in splinting, only the minimum immobilization must be used. Parts uninvolved must be kept free so that they can be exercised. One of the most troublesome complications of fractures of the upper extremity — the "frozen shoulder" due to carrying the arm in a sling — can be readily avoided if the patient simply lifts his arm over his head in flexion and abduction several times a day. This can be done without risk in fractures, once the part is adequately immobilized.

If there is persistent swelling of a part, the excess lymph in the tissues leaves a deposit of fibrin that, in time, is replaced by granulation tissue. Granulation tissue is scar tissue, and scar in the vicinity of a joint means loss of motion particularly if the joint requires immobilization. This is of the utmost importance in injuries of the hand and wrist, in which swelling of the fingers is likely to occur. When such injuries require splinting, only the minimum splinting must be used. Casts applied for injuries of the forearm and wrist should not extend beyond the distal palmar crease, so that the fingers can be mobilized. When fingers must be splinted the position of flexion should be used whenever possible to put the collateral ligaments of the fingers under tension. To allow the ligaments to stiffen and contract in the position of extension means long and tedious work in the restoration of flexion. About 25 per cent of cases at the Liberty Mutual Rehabilitation Center are hand injuries, and many of these patients are under treatment for stiffness of the fingers that, with proper immobilization, could have been avoided.

When the lower extremity requires immobilization, muscle tone can still be largely preserved by

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the simple process of muscle setting within the splint or cast. This can be done without jeopardizing the healing process in all conditions, with the possible exception of fresh tendon sutures.

By exercising the body as a whole while the patient is in bed and by exercising uninvolved parts and by muscle-setting exercises while he is in splints, much can be done to preserve general and local muscle tone and joint mobility during the period of recumbency or immobilization.

When the patient is freed of all apparatus and is ambulatory the job is by no means over. This is in all probability the most critical period of all, because failure to use the injured part can still nullify all the good work done in the period of immobilization. When a patient is at home he is no longer under complete supervision and is apt to neglect his exercises. Trips to the doctor's office three times a week for baking and massage make a dangerous rut for the patient to get into. Between these trips he is likely to do nothing for himself and to let the physician or a physiotherapist do the work for him.

Patients must be made to understand that the doctor or his physiotherapist can aid them in the restoration of strength and motion, but that the actual work must be done by themselves. Exercises must be performed even though they cause some discomfort. However, it is the duty of the physician to make sure that a definite course of action is adopted and understood. The patient must know exactly what exercises he is to do, how long he must do them and why he is doing them. Too often, progress is slow because the patient does not do the exercises properly if at all. This is often due to the fact that the doctor has not given sufficient instruction and has not checked to see that the instructions have been carried out. Routine gymnastic exercises are dull and uninteresting, and often do not accomplish the desired result. Exercises in the form of work therapy are much more beneficial. A patient with a saw and hammer can accomplish more for himself in one week than all the baking and massage can perform in months. Work or occupational therapy is a form of treatment that has been completely overlooked and that everyone interested in the treatment of traumatic lesions must learn. Occupational therapy does not mean the making of leather belts, pocketbooks and so forth, which have a place in some conditions but are chiefly diversional and of little value to the average worker, but actual work designed to restore to the patient motions essential in his trade. Frederick J. Cotton once said, "The best way to restore a bricklayer to his job is to make him lay bricks." This statement is undeniably true, but such therapy is not always so simple as it sounds.

Patients who have had prolonged and painful disability are apt to suffer from mental depression or loss of morale. Failure to notice improvement favors the development of many psychogenic factors,

particularly an anxiety state. Fear of being unable to return to their regular work and fear that they have lost their jobs after a prolonged convalescence are common causes of mental depression and loss of morale. This state is aggravated by domestic and financial difficulties, brought on by the loss of earning power. Occasionally, this condition is precipitated or aggravated by the development of the menopause. Such patients are extremely difficult to rehabilitate. They need encouragement and must often be convinced that they are not quite so badly off as they think. For such a person there is no better treatment than work therapy.

Dissatisfaction with present methods of treatment and encouragement offered by the rehabilitation program developed in England during the war brought about the establishment of the Rehabilitation Center by the Liberty Mutual Insurance Company in June, 1943. In the past four years we have become convinced of the value of a combination of physiotherapy and occupational therapy, and the decided advantage of keeping the patient busy all day long for five days a week.

When a patient is admitted to the Center a complete appraisal is made. The exact extent of the injuries is determined. If it is believed that he can be rehabilitated, that further surgery is not indicated and that the general physical condition is satisfactory, treatment is started.

Usually, the patient is sent first to the physiotherapy department, which is completely equipped with the usual armamentarium of infrared lamps, diathermy, whirlpool baths, paraffin baths, stall bars, chest weights, Kanavel tables, graduated stairs, resistance bicycles, rowing machines and so forth. Here he is placed on daily exercises that are performed under supervision.

When he has improved sufficiently he is sent to the occupational-therapy department, where he is given work to exercise the disabled part. Tools and sanding blocks are constructed to fit the individual needs of the patient. All work is planned and supervised. Care is taken not to exceed the fatigue point. At first only light or sedentary work may be done. As the work tolerance increases, the work load is increased. Since most of these patients are unskilled, woodworking is the chief means of work therapy. No motor-driven tools are used. Jig saws are operated by sewing-machine or bicycle jigs. For ankle injuries the sewing-machine jig and for knee injuries the bicycle jig are used. Foot-operated grinding wheels are also of value. For shoulder injuries suspension slings aid in elevation of the arm. When a shoulder has improved sufficiently a hand-operated printing machine is of value. Painters are allowed to paint and thus to exercise their shoulders, hands and wrists. There is a complete machinist's outfit. Logs for sawing and a sand pit are used to build work tolerance in laborers. Hand saws, planes, files and the usual carpenter's equip-

ment are of great value in restoring lost motion and muscle power, especially in the upper extremity. To keep the patient's interest, definite work projects are created. The building of such objects as end tables, sewing cabinets, tool boxes, rocking horses, carts, chairs and magazine racks holds the patient's interest. Knot tying, rug making, modeling in plaster and work carving are of value in hand cases. All work can be done at any level and in any plane,

psychologically. It is not uncommon for patients to say, "If I can do this work I can do my own." Most patients, convinced in their own minds that they can return to work, need no further stimulus to do so.

The following statistics give some idea of our success (Table 1). In the past four years 666 cases have been treated. Of this number there were 540 male and 126 female patients. The average

TABLE 1 *Results of Therapy at Rehabilitation Center, Liberty Mutual Insurance Company from June, 1943 to April, 1947*

TOTAL PATIENTS	MALE PATIENTS	FEMALE PATIENTS	AVERAGE AGE		AVERAGE INTERVAL FROM INJURY TO ADMISSION	AVERAGE PERIOD OF TREATMENT	PATIENTS RETURNED TO WORK	
			MALE PATIENTS	FEMALE PATIENTS			NO.	PERCENTAGE
666	540	126	37 46	37 43	mo 6.5	da. 42	368	65

so that any lost motion and any atrophied muscle group can be restored.

When a patient has reached his work tolerance he is allowed to rest. At that time he can listen to the radio and, especially in the summer months, to the ball games.

After the rest period he is sent to the recreational-therapy department. He may play pool, ping-pong, horseshoes, darts, checkers and so forth. Recreational therapy is also designed to aid in the restoration of lost motion. For example, checkers may be played on the floor, on a table or on the wall. Ping-pong has been found to be of considerable value in the training of patients with upper-extremity amputations. The agility that can be developed in a short time by this means is remarkable.

The patient, it can be seen, is kept busy all day long for five days a week. The building of articles in the workshop is a tremendous stimulus and does much to raise morale. Patients become so engrossed in their work that they must be carefully watched so that they do not become fatigued. Women are as enthusiastic as men. A spirit of competition is developed between patients with similar injuries. Disgruntled and discouraged patients soon enter into the swing of things and rapidly lose their complaints. Under such a regime most patients make progress both physically and

age is higher than one would expect, being forty-six years for men and forty-three years for women. Most of these patients had multiple and serious injuries. With such injuries, in this age group, the earlier treatment is started, the better the result. In the average case, however, six and a half months had elapsed between the date of injury and admission to the Center. Much valuable time had thus been lost. Atrophy, joint stiffness and loss of morale have usually been well advanced and have been serious handicaps to overcome. Despite this fact, however, 368 patients, or 65 per cent of all patients admitted, have returned to gainful employment. The average length of treatment required has been forty-two days.

Considering the seriousness of the injuries, the age of the patients and the extent of the complications produced by the lack of efficient treatment for six and a half months, it is doubtful that many of these patients could have been rehabilitated by any other means.

Our experience has convinced us of the value of a combination of physical therapy and early work therapy. With the education of the medical profession in the procedures of treatment and after-care described above, it is believed that a far greater number of seriously injured workmen will be restored both to industry and to their families.



## MEDICAL PROGRESS

### CUTANEOUS MEDICINE

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BOSTON

THE skin pictures the general health of the patient much better than any other organ. Age is reflected in the pink bloom of infancy, the oiliness and pasty appearance of adolescence, the disfiguring yellowish spots and telangiectasia of middle age and the wrinkled, thin, overstretched and dry appearance of old age. Physicians of previous generations trained their powers of observation and palpation and carefully studied changes in the skin and mucous membranes, many diagnoses of systemic diseases resulted from their keen perception. Today, physicians fail to make use of these facilities and depend too much on mechanical devices and laboratory procedures, many of which are irrelevant or unnecessary, they piece the data together like a picture puzzle.

Fortunately, many clinicians exercise their powers of observation of the skin, for they have learned that such study yields important clues in the diagnosis of systemic disease. Bacteriologists, pathologists, roentgenologists and even anatomists are showing increased interest in dermatology.

An anatomist states that a clinician displays keen clinical discernment when he regards the skin as an index to visceral change as well as subject to dermatologic conditions. To adopt this point of view is to accept the embryologic fact that the skin is an exposed part of the depressed central nervous system or, conversely, that the central nervous system is a depressed part of the skin. Thus, itching or seborrheic dermatitis may be due on the one hand to a specific dermatologic condition and on the other hand to an inherited predisposition of the autonomic nervous system, the gonadal system or the central nervous system. It is this developmental point of view that makes possible the consideration of the skin as an integral part of the organism.<sup>1</sup>

No one believes that systemic disease can be diagnosed entirely from the skin, but careful observation can be extremely valuable. Redness of the face may suggest an irritable heart, capillary and arterial pulsation, an aortic insufficiency, cyanosis of the face, a paroxysmal tachycardia, malar flush, a yellowish forehead and blue lips, a mitral stenosis, and petechial spots and pinkish, tender macules on the fingers and toes, an endo-

carditis. The earthy hue of the skin tinged with blueness suggests an emphysema.

Many a systemic disease produces a cutaneous change in the initial or final stages. Many a clinical report starts with the statement that the patient first noticed spots on the skin. These occur so frequently and disappear so rapidly that they may have no clinical significance, except to suggest a certain category of disease, especially the infections. In fatal diseases the skin may give the first warning, as in pruritus or the pigmentary eruptions often seen with internal malignant tumors. Later, the inflammatory lesions may precede metastases. A patient under observation following extirpation of the vulva for removal of a cancer showed nodules and later small bullae preceding a necrotic crusted center that histopathologically revealed carcinomatous changes.

The dermatologist has known for centuries that, apart from the dermatitides due to chemical irritants, parasitic infestations and bacterial and fungous infections, most cutaneous diseases are associated with systemic disturbances and that many systemic diseases affect the skin. A dermatologist must have the diagnostic acumen of the internist as well as the patience and therapeutic skill of the "externist." He realizes that treatment must be not only local but also systemic if the contributing or precipitating cause is to be removed.

#### GENETICS

Abnormalities due to defects of the germ plasm may manifest themselves very early. In albinism a deficiency in pigment may be complete or incomplete. Xeroderma pigmentosa may be suspected by the photophobia noticed in the first few weeks of life and later by erythema, pigmentation, freckles, atrophy, telangiectasia and malignant growths. Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber's syndrome) may affect several members of a family.<sup>2</sup>

Photodermatitis, with or without circulating hematoporphyrin, is receiving considerable discussion, and it is now fairly well recognized that the porphyria is the result and not the cause of the dermal sensitization.<sup>3</sup>

Lipoid proteonosis is a familial disease first described in 1929 by Urbach.<sup>4</sup> It begins in infancy,

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with hoarseness and inability to cry. Various skin-colored, nodular, hyperkeratotic or warty lesions appear on the face, extremities and mucous membranes. Hypertrophic plaques may be present on the elbows and knees. Diabetes is sometimes associated with this disease. The blood lipoids are essentially normal, but there is a disturbance of the phospholipids.

I have seen xanthoma tuberosum multiplex in more than one member of a family. It is due to a hypercholesteremia of the blood, and the patient usually presents yellowish nodules on the buttocks and extensor surfaces. Other members of the family may have diabetes or hypercholesteremia, or both.

Disturbances of the elastic tissue manifest themselves in hyperelasticity and fragility of the skin, hyperelasticity of the joints, pseudo-tumors following trauma and subcutaneous nodules (cutis hyperelastica, Ehlers-Danlos syndrome), and deficient elastic tissue is seen in epidermolysis bullosa. This condition may vary from a mild disturbance of the skin with the occasional bullae following trauma to a severe type with not only cutaneous and mucous membrane lesions but also loss of hair and low intelligence. It may produce such severe systemic disturbances as to mislead dermatologists into describing the disease under another name.

Danbolt and Closs<sup>4</sup> classified 2 cases by the title "akrodermatitis enteropathica" and attributed the affection to disturbances of the gastrointestinal tract. The disease is characterized by a pustulous dermatitis, which is frequently familial and appears in early childhood, often after weaning. The dermatitis is preferentially located around the natural openings of the body and on the protruding parts of the head, trunk and extremities (hence the term "akrodermatitis"). The terminal phalanges of the fingers are swollen, and there is pustulous paronychia and atrophy of the nails. Furthermore, there are total alopecia, photophobia and blepharitis and sometimes affections of the mucous membrane of the oral cavity (papillomas of the tongue). The disease tends to be chronic, with recurring exacerbations, during which there is diarrhea with foamy, foul-smelling, pale yellowish-gray stools. The calcium and phosphorus content of the urine is pronouncedly diminished.<sup>5</sup>

The above disease is the severe type of epidermolysis bullosa originally described by Wende<sup>6</sup> in 1902, when he reported a case presenting unusual features. The chief characteristics were as follows: evidence of formation of vesicles and blebs at points subject to trauma and irritation, marked infiltration of the skin after the lesions subside, arrangement of the bullae in concentric patches, decided changes in the nails, lack of hair growth on the scalp and absence of eyelashes and eyebrows, and general tenacity of the skin. I have observed 2 children with this disease both of whom died. One showed pathogenic yeast cells on the peroral and perianal skin.

Keratosis follicularis (Darier's disease) has received more than passing interest because of claims for cure by the administration of vitamin A. I have observed no such cure in my cases, although all patients showed temporary improvement. This disease, which is transmitted by a single dominant, is usually limited to two generations because of infertility.

Thannhauser<sup>7</sup> disagrees with Cole's diagnosis of congenital ectodermal dysplasia associated with congenital cataracts. The former believes that the cases described are examples of Rothmund's syndrome due to defects of the entire germinal plasma. Cole<sup>8</sup> retaliates by citing Thannhauser's report of a typical anhydrotic type of ectodermal dysplasia with low fasting blood sugar, a flat sugar-tolerance curve and low blood pressure (disturbance of the adrenal medulla). Roentgenograms showed exostoses of the tables of the skull.<sup>9</sup> Osseous tissue is of mesodermal origin, and this case was not one of purely congenital ectodermal dysplasia of the anhydrotic type. Cole<sup>8</sup> states that he had difficulty in putting such a case under the proper heading from the developmental standpoint if the term "congenital ectodermal dysplasia" is to be used. Good proof of this contention is afforded by the fact that it is difficult to separate the ectoderm from the rest of the anatomy.

Carleton<sup>10</sup> described a case that was stated to be one of poikiloderma vasculare atrophicum, associated with cataracts (Rothmund's syndrome). Scleropoikiloderma has been mentioned as one of the characteristics of Werner's syndrome. Thannhauser,<sup>10</sup> however, believes that the features of the skin changes are different in both syndromes. In Werner's syndrome the most striking characteristic is tightening of the skin over the underlying structures, which are very poor in subcutaneous fat tissue. Ulcers develop mainly on the points of pressure on the heels and toes, over the ankles and especially over the Achilles tendon.

Moehlig<sup>11</sup> reports a case of progeria (premature old age) with severe dwarfism and congenital cataracts in a five-year-old boy who, although mentally retarded, had an unusual talent for music. This condition (Werner's syndrome) is seen in adults, and the cases are thought to be due to multiple germ defects.<sup>11</sup>

Neurofibromatosis (Von Recklinghausen's disease) has been traced by Frank<sup>12</sup> through five generations. This is a familial disease in which the defect may be transmitted in the same pattern—namely, one family showing areas of pigmentation and others, tumors of various size present also in the peripheral nerves. It may be associated with alopecia, feeble-mindedness, epilepsy and dementia praecox. The pathogenesis of osteitis cystica localisata and disseminata is closely related to neurofibromatosis. Recklinghausen and its osseous manifestations.<sup>12</sup> Von Recklinghausen's disease is a fairly common

one, which manifests itself in many strange combinations — for example, pigmentation and scoliosis. Its etiology and pathology are still open to discussion. Bourneville's disease occasionally resembles neurofibromatosis. The patient shows reddish, warty tumors, with feeble-mindedness or epilepsy. The tumors on the skin are of the adenoma sebaceum type, and these lesions may appear in the brain, heart or kidneys, resulting in death.

### ENDOCRINES

Many dermatologic manifestations have been attributed to endocrine dysfunction. A definite relation has been established in a few but has not been proved in others. The former are those associated with Addison's disease, adrenal tumors, Simmonds's disease, Cushing's syndrome, Frölich's syndrome, the Lawrence-Moon-Biedl syndrome and pancreatic disease. The others range from urticaria to psoriasis. As the result of improvement coincident with or subsequent to hormonal therapy, entities ranging from hypertrichosis to lupus erythematosus have been considered as due to endocrine diseases. Many apparent cures have not been corroborated.

Acne occurs with sufficient frequency in conjunction with changes in the endocrine system — as at adolescence, or with tumors of the adrenal cortex and arrhenoblastoma and also during the administration of androgens — to postulate a relation, but therapy as the result of these observations has not been too successful. Pruritus vulvae, kraurosis vulvae and leukoplakic vulvitis are apparently related to estrogen deficiency, but the clinical response is not startling. Hyperkeratitis (keratoderma) of the palms and soles associated with menopause may respond dramatically to sufficient estrogens. The pigmentation of the skin and mucous membranes in Addison's disease is characteristic and clears with suitable therapy. Calcinosis, local or generalized, may appear with hyperparathyroidism. Many cutaneous lesions have been attributed to diseases of the thyroid gland.

The dermatologist may be the first to diagnose myxedema. First consulted for loss of hair, he may note the dry, yellowish, waxy appearance of the skin, with extensive telangiectasia on the cheeks producing abnormal redness. The hair is dry, brittle and sparse, with considerable loss of the eyebrows, especially at the outer third. A lowered basal metabolic rate and a high cholesterol content confirm the diagnosis. Lange<sup>14</sup> states that the presence of edema in the skin of patients suffering from myxedema and the tendency to generalized serous effusions are so far physiologically unexplained. Five cases of myxedema all showed a marked increase in capillary permeability. With thyroid therapy the permeability rapidly returns to normal, simultaneously with a marked diuresis.<sup>14</sup> Amersbach and Kanee<sup>15</sup> reported that localized myxedema of the tuberous variety developed in a

patient who had been suffering from exophthalmic goiter for four years and who had persistent hyperthyroidism, despite protracted therapy, including two thyroidectomies.

Pillsbury and Stokes<sup>16</sup> have described circumscribed forms of the disease. They analyzed 22 cases in the literature and 1 case of their own of circumscribed myxedema of the skin, and divided them into two classes: those characterized by nodular infiltrations variously distributed on the face, arms, back and scrotum, and those in which the manifestations of the skin are invariably associated with exophthalmic goiter. A tuberosc nodular or papular type and a plaque type of myxedema of the skin involving the pretibial region are recognized.

O'Leary<sup>17</sup> reported a number of cases of localized solid edema of the extremities in association with exophthalmic goiter. In the majority of cases circumscribed myxedema follows thyroidectomy, appearing simultaneously with the signs and symptoms of recurrent hyperthyroidism. Sunseri<sup>18</sup> agrees that it may develop before thyroidectomy or before or during the active manifestations of thyroid intoxication.

The assumption that the thyroid hormone plays a role in the healing of wounds was corroborated by the fact that wounds heal poorly and sometimes not at all in myxedematous patients. Eppinger<sup>19</sup> first used aqueous extracts of thyroid gland mixed with lanolin, and then found that pulverized thyroid substance simply strewn into the wound was quite as effective. He believes that many torpid cutaneous ulcers are due to local myxedema.

I have noted an extensive isinglass scaling on the anterior aspect of the lower legs of several women with hypothyroidism. In hyperthyroidism the dermatologist may observe a markedly flushed, terrified, emaciated person whose skin is soft, oily and moist, hyperhidrosis and urticaria may be the chief complaints. Lichen planus with recurrent attacks associated with exacerbations of hyperthyroidism was reported by Ebert and Otsuka.<sup>20</sup> A patient with hyperthyroidism may be so sensitive to sunlight that exposure of a few minutes produces severe reddening of the skin and blistering.

Just as the appearance of the patient with myxedema is easily recognized by the physician, so also is that of the acromegalic patient. The skin of the sufferer from pituitary dysfunction, however, may be raised in folds, especially in the scalp, causing cutis verticis gyrata. Weber<sup>21</sup> stresses this relation and tabulates 12 cases. The hair is thick and coarse, as is the skin, which may be pigmented and freckled owing to melanin, especially in women. The plethoric skin, together with reddish or purplish abdominal striae, and painful adiposity should suggest Cushing's syndrome.

Within the past two years I have seen 2 cases of Simmonds's disease (pituitary cachexia), 1 in a

man, although most cases occur in females. Before death the patient showed complete loss of hair. Although he was in his late forties, the skin was smooth, thin and as delicate as a baby's, with a pale yellowish waxy color. The other patient showed a dry, coarse skin typical of hypothyroidism, with sparseness of the hair and with vegetating, crusting and scaling of the eyebrows, nose and lower legs. The plaques on the lower legs were finally cast off like pieces of bark from a tree. The diagnosis was made by laboratory findings, and therapy resulted in remarkable recovery.

Without corroboration, many diseases, including furunculosis, acne and psoriasis,<sup>22</sup> have been attributed to disease of the pancreas. A routine urinalysis is a necessity for a complete dermatologic diagnosis when there is only the complaint of pruritus. Deficiency of the islets of Langerhans may result in many cutaneous entities, such as necrobiosis lipodica diabetorum, xanthomatosis diabetorum and hemochromatosis and such nonspecific manifestations as gangrene, ulcers and bacterial and *Monoilia* infections.

Urbach<sup>23</sup> has recently suggested the term "skin diabetes" to designate the syndrome of "therapy-resistant skin disease (generally presenting the clinical picture of furunculosis, sweat gland abscesses, eczema, pruritus), high fasting skin sugar level together with a normal blood-sugar curve, and pronounced improvement of the dermatosis, as well as fall in high skin sugar level on a low carbohydrate diet, sometimes combined with insulin." His conclusion is as follows:

Quite aside from the question as to whether or not cases presenting independent cutaneous glycohemostasis are actually to be regarded as cases of skin diabetes, it may be safely said on the basis of clinical experience that a diabetic diet should unhesitatingly be tried in cases of therapy-resistant skin diseases such as furunculosis, eczema, or pruritus, even when the blood-sugar tolerance test is normal.

Sheppard<sup>24</sup> has reported stomatitis, burning, ulceration, dryness and many tongue symptoms.

### ALLERGY

Allergy has become a too popular word in dermatology and medicine. It is time to review von Pirquet's<sup>25</sup> original article, in which he states

We need a new, general and unambiguous word for the change of condition which the organism undergoes through contact with some organic, animate, or inanimate poison. The vaccinated person is in a different relation to the pox or lymph, the syphilitic, in a different relation to the syphilitic organism, the tubercular person in a different relation to the tuberculin, and the person injected with serum in a different relation to the serum than are the individuals who have not yet come in contact with the agent concerned. Nevertheless he is still far from being sensitive. All that we can say of him is that his capability of reaction is changed. For this general idea of changed reaction capability I propose the word allergy (allotia designates the deviation from the original setup, that is, the deviation from the normal conduct). The vaccinated one, the tubercular, the person injected with the serum are

with regard to their respective foreign bodies allergic. A foreign body, on the other hand, which influences the organism by means of incorporation (one or several times) to a change of reaction is an allergen. To the allergens belong not only the antigens but also the numerous albuminous bodies which cause no antibody formation but cause hypersensitivity. All indices of infection sicknesses which are followed by immunity are allergens.

Several years ago, after listening to a symposium on allergy and dermatology, I defined allergy as follows: "In the field of practical dermatology, allergy is an intellectual hobby limited only by one's powers of expression, oral or written."<sup>26</sup> The term "allergy" may be accepted according to the definition of a specific altered capacity to react if the causative factors can be specified, as in cases of bacterial infections.<sup>26</sup> "Allergy" is rapidly becoming a huge wastepaper basket into which many diseases of unknown etiology are being tossed — a catch-all phrase like "eczema" or "rheumatism."

Periarteritis nodosa, a disease of unknown etiology, is now attributed to allergy or hypersensitivity because after a single positive exposure the patient died and autopsy showed arterial lesions similar to those of periarteritis nodosa. It is interesting to read the various editorial comments in the *Journal of the American Medical Association*. One of these states that periarteritis nodosa has generally been regarded as a rare disease, probably infectious, which almost always ends fatally and has rarely been diagnosed in vivo.<sup>27</sup> The chief histologic feature is a necrotizing lesion on the arterial wall with a surrounding inflammatory reaction. The diagnosis is difficult except in the rare cases that exhibit the characteristic subcutaneous nodules with the characteristic histologic changes in the blood vessels. Periarteritis nodosa has been attributed to syphilis, to a filterable virus, to various infections, to toxic injuries and to disease of the central nervous system. Gruber was among the earliest investigators to suggest that the condition was due to hypersensitivity.<sup>27</sup> The recent observations of Rich<sup>28</sup> and of Rich and Gregory<sup>29</sup> add support to this theory.

In 1942 Rich<sup>28</sup> reported autopsies on 5 patients who had had serum sickness shortly before death, in all of whom vascular lesions characteristic of periarteritis nodosa were demonstrable. None of the patients had any symptoms suggestive of periarteritis prior to the acute terminal illness, and all the vascular lesions were fresh. Similar vascular lesions were demonstrated in 2 patients who had had reactions to sulfonamide therapy.<sup>28</sup> Rich concluded that vascular lesions of the periarteritic type can be a manifestation of the anaphylactic type of hypersensitivity.

In the following year Rich and Gregory<sup>29</sup> reported the experimental production of similar lesions. Rabbits were sensitized with one or more large doses (10 cc) of horse serum. All the animals on skin test the immediate anaphylactic

type of hypersensitivity, some developing Arthus reactions with necrosis. They were sacrificed at periods ranging from seventeen to twenty-six days, and the majority showed arteritic lesions characteristic of various stages of periarteritis nodosa. In an extension of this experiment the authors<sup>31</sup> found in the hearts of 11 of 36 similarly sensitized rabbits lesions that reproduced closely the five supposedly pathognomonic features of acute rheumatic carditis. Caution in interpreting these experiments is suggested by the reports of periarteritis developing in rats and dogs made hypertensive by clamping of the renal artery<sup>32</sup> or by wrapping of the kidney in silk.<sup>33</sup>

Another editorial states that the function and purpose of the allergic reactions are receiving close attention and that some attempt is being made to apply the result of laboratory experiments to patients.<sup>34</sup> The increased understanding of tissue reactions is a step forward. Concerning the allergic subject, however, it is not yet certain that the variation from the normal depends on anything more than a quantitative change.

An interesting clinical entity was described in 1932 by Loeffler. Miller<sup>35</sup> reported a case and stated that only 4 such cases had been reported in this country. The most important criteria for diagnosis, he asserted, are the symptoms and signs of pulmonary disease, the extent and character of pulmonary involvement, the transient character of the pulmonary shadows, eosinophilia and seasonal and sex variation. X-ray examination usually reveals a more extensive pulmonary involvement than was suspected from the clinical examination. The eosinophil count usually ranges between 15 and 35 per cent but has in some cases exceeded 60 per cent. The pathology of this disease is unknown, since no clear-cut fatal case has come to autopsy. The etiology of the disease is also uncertain. Most authorities describe the syndrome as an allergic response of the pulmonary tissue that may be induced by various allergens.

There must have been deaths later from this disease, for it is stated that the changes in the few cases examined after death appear to support the allergic explanation.<sup>36</sup> It is further pointed out that granulomatous processes in other organs, such as eosinophilic granuloma of bone, may also be allergic.<sup>37</sup>

In Weidman's excellent article on eosinophilic granulomas of the skin he considers their relation to Loeffler's syndrome. The journals of tropical medicine are outstanding in their reports of this disease because animal parasites (ranging from ascaris to ameba) are the occasion for the eosinophilia. Hodes and Wood<sup>38</sup> called it "tropical eosinophilia." Indeed, the injection of extracts of ascaris has proved the eosinophilogenous role of these parasites through the mechanism of allergy. The interstitial tissue (not the bronchi) is the shock organ.<sup>39</sup> Animal parasites, however, are not always demonstrable, notably in the cases in Palestine and those in which cutaneous

manifestations were associated. Cutaneous involvement has been established by Lyon and Kleinhans,<sup>40</sup> who reported 20 cases in Jerusalem in six months, although several patients did not exhibit pulmonary lesions. They cited other authors who spoke of "eosinophilic erythroedema," "eosinophilic disease with cutaneous manifestations" and eosinophilia in the sternal bone marrow in addition to the other lesions. Substantially, the dermatosis is a diffuse erythema multiforme perstans in large patches, affecting both the skin and the oral mucosa, and often migrating. In any event, a new message has come to dermatologists. Patients with persistent erythema multiforme lesions (including migrating ones) demand study regarding the possibilities of Loeffler's syndrome.<sup>41, 42</sup> Pujol<sup>43</sup> reports a case with dermatitis in Brazil.

I believe that if physicians keep this disease in mind many cases will be found. Within six months I have seen 2 cases that suggested it. The biopsy in each case showed no eosinophilia. The first patient was a three-year-old girl with a history of a more or less generalized eruption of three weeks' duration. The eruption consisted of raised, circinate plaques involving the arms, lower trunk and legs. Superimposed on several of the plaques were vesicles and small bullae. The patient also had a history of frequent asthmatic attacks and showed pediculosis of the scalp. The white-cell count was 17,500, with an eosinophil count ranging around 24 per cent. X-ray examination of the chest showed extensive mottling.

The second patient, a twenty-three-year-old man, was admitted to a tuberculosis sanatorium because of an x-ray diagnosis of tuberculosis. Repeated x-ray examination suggested sarcoid. Six weeks later the x-ray findings were essentially negative. The first examination revealed a half-dollar-sized erythematous wheal on the lower portion of the chest. This persisted, and three weeks later similar lesions appeared on the left arm, forehead, abdomen, buttocks and thighs. A diagnosis of erythema multiforme perstans was made. Three months later the eruption had disappeared, leaving pigmented areas. Laboratory studies were negative except for a white-cell count ranging from 13,500 to 29,000. There was a persistent increase in the percentage of eosinophils, ranging at times from 20 to 55 per cent. Sternal puncture showed marked eosinophilia, and nasal polyps removed were markedly infiltrated with eosinophils. This case is interesting because it has been stated by some authors that the roentgenographic appearance of the process is often not unlike that of tuberculosis.<sup>44</sup>

#### RHEUMATIC DISEASES

According to Campbell et al.<sup>45</sup> erythema multiforme and erythema nodosum are not specific lesions of rheumatic fever. The most frequent type of eruption is found on the trunk, upper arms and legs.

The lesions, which are macular and from 1 to 2 cm in diameter (occasionally larger), appear as bright-pink circinate or gyrate areas. They become more prominent after a few minutes' undressed exposure and vary from day to day. Red, elevated, edematous plaques may be seen over the affected joints. The cutaneous lesions appear after the joint manifestations. Subcutaneous nodules attached to tendons, ligaments and fascia over the elbows, knees or other joints may remain for several weeks and suggest a severe infection. Purpura and urticaria are not infrequent findings. Skin lesions in rheumatic fever do not help in deciding when rheumatic activity ends, they are merely acute manifestations occurring in a persistent disease.

Perry<sup>46</sup> studied 112 patients — 38 males and 74 females. The material reviewed offers little support to the theory that erythema nodosum is a manifestation of acute rheumatic fever. Perry agrees with those who have held that erythema nodosum must be regarded as the result of a nonspecific reaction to a variety of infections or toxic agents and that it is not a specific disease. It is clear, however, that these agents give rise to the syndrome only in patients constitutionally predisposed to it.

The relation between psoriasis and arthritis appearing before, during or after the appearance of the psoriatic lesions is a well established finding. The arthritis may respond to proper treatment of the psoriasis.

In a recent article Mallory<sup>47</sup> cites the hypothesis advanced by Rich that the lesions of periarteritis nodosa and rheumatic fever are the result of anaphylactic hypersensitivity.<sup>48</sup>

Sargent<sup>48</sup> reports 3 cases of Reiter's syndrome, the etiology of which is completely unknown. This disease of dramatic proportions is characterized by extensive lesions of the joints, mucous membranes and skin. It is exceedingly protracted in its course sometimes reactivating after prolonged periods of remission, but tending to spontaneous recovery. It is utterly refractory to all known treatment, except perhaps as it may be mildly benefited by such indirect stimulative and supportive methods as local physiotherapy, fever therapy and whole-blood transfusions.

Reiter<sup>49</sup> first described this disease as being characterized by arthritis, urethritis and conjunctivitis not caused by gonorrhea. In 1942 Bauer and Engleman<sup>50</sup> first reported it in the American literature with their series of 6 cases. In 1944 Lever and Crawford<sup>51</sup> followed with a report of 2 cases, the second of which (the only case so far reported in a female) left them in doubt regarding its proper classification.

Although in many cases the clinical picture is one of average chronic polyarticular arthritis associated with mild and fleeting inflammation of the mucosa of the eye and genitals, when Reiter's disease is in full bloom a low-grade fever is present,

lesions of the buccal mucosa and of the epidermis occur, its mild conjunctivitis becomes an extensive iritis and keratitis, its arthritis settles in several joints and is of deforming proportions, sometimes ending in ankylosis, and its urologic manifestations extend to widespread superficial ulceration of the glans penis and even the urethral and bladder mucosa, causing discharge, pyuria and protracted severe cystitis. Yet the disease is completely devoid of any bacterial basis demonstrable by smear, culture, skin test and complement-fixation test or dark-field examination. Two patients whose cases were reported were attached to the same construction battalion, and their duties led to rather close association over periods of eight and nine months, respectively, prior to the beginning of the illness. The disease strongly suggests an infectious cause. Further study may prove that it falls into the ever-growing group of virus diseases. Idiopathic blennorrhoeal arthritis is suggested to give a fairly descriptive terminology to this little-known disease and to escape the use of a proper name.<sup>48</sup>

In 1945 Rosenblum<sup>52</sup> reported 10 cases of Reiter's syndrome in personnel of the United States Navy, of which 5 arose in the South Pacific and 5 in the United States. One patient had a widespread, acute skin eruption resembling erythema multiforme.<sup>53</sup> I recently treated a severe case at the United States Public Health Hospital in Brighton. The patient, a young man who had conjunctivitis, urethritis and arthritis, presented lesions in the axillary and genitocrural regions consisting of small bullae. Vesicles and bullae appeared on the palms and soles, and the eruption later became a dermatitis exfoliativa with complete loss of hair. The skin and hair became normal in several months, with complete recovery, and there was no limitation of joint motion.

#### METABOLISM

Numerous articles describing cutaneous manifestations of nutritional disturbances have recently appeared. In 1888 Gee published a classic description of idiopathic steatorrhea. In this affliction skin lesions are frequent and diversified, they may be pigmented patches, psoriasisform plaques, eczematous areas or pustular dermatitides. The combination of skin lesions, infantilism, anemia, osteomalacia, tetany, dilatation of the colon and fatty stools may be found in a patient suffering from celiac disease.<sup>54</sup>

There are four centuries intervening between the scurvy of the days of the Crusaders and the beginning of our present-day knowledge of the subject. Impetiginous eruptions were described nearly two hundred years ago, in 1763 Cutaneous avitaminosis in children has been reviewed by Ormsby et al.,<sup>55</sup> who state that the lesions due to vitamin A deficiency are similar to those found in adults, except for lichen spinulosus, which is found exclusively in children and

is characterized by minute papules situated over the pilosebaceous follicles, each with a projecting horny spinule. Pellagra is usually less marked in children. With all the literature on avitaminosis one wonders why more skin diseases from nutritional deficiencies were not reported from concentration camps. Parasitic diseases were frequent, but pictures of starved prisoners showed no evidence of cutaneous manifestations. Some cases of pellagra, however, were reported. Among war prisoners in Java and Sumatra, the localization of true pellagra pigmentation was usually on the back of the hands and the feet and on the dorsal skin, sometimes the hair turned from spotless black to gray in three months.<sup>56</sup>

Chavarria et al.<sup>57</sup> report that hair disturbances have been noted in children, especially in the severe forms of vitamin A deficiencies, pellagra, riboflavin deficiency (cheilosis), nutritional edema, beriberi and the mixed forms of these general groups. They exhibit characteristic, associated changes in the hair, including both loss — diffuse or especially pronounced in the frontal area — and depigmentation. Biotin is thought but not proved to accelerate over other therapies the return to normal growth and pigmentation of the hair.<sup>57</sup> In the Medical Survey of Nutrition in Newfoundland note was made of a form of change in the hair — namely, a dry, lack-luster hair, so-called "staring hair."<sup>58</sup>

The subject of the relation between the so-called "rosacea keratitis" and cutaneous rosacea has been debated a bit acrimoniously. A riboflavinosis due to the vitamin B<sub>2</sub> deficiency is well known. There is considerable disagreement among the ophthalmologists themselves and the dermatologists regarding ocular disturbances. This was stimulated by a paper published in 1939 on the effect of experimental riboflavin deficiency on corneal vascularization in rats.<sup>59</sup> In 1940, after observing the relief of excessive corneal vascularization in 36 patients, although only 9 showed some type of cutaneous disturbance, Johnson and Eckardt<sup>60</sup> made a diagnosis of rosacea keratitis. In June, 1940, Sydenstricker et al.<sup>61</sup> reported a careful survey of 45 patients in whom they found this same type of corneal vascularization, originating at the limbic plexus and extending centripetally, originally described by Bessey and Wolbach.<sup>59</sup> Sydenstricker labeled this eye disease dietary keratitis, but in November, 1940, Johnson<sup>62</sup> claimed rosacea keratitis to be identical with dietary keratitis. He reiterated this a year later<sup>63</sup> but admitted that rosacea is a poor term since the condition is not caused by acne rosacea. Subsequently, two papers, one by an ophthalmologist (Fish<sup>64</sup>) and another by a dermatologist (Wise<sup>65</sup>), and later a statement by Johnson<sup>66</sup> that the appearance of keratitis with acne rosacea is a coincidence, fairly well established the fact that the term "rosacea keratitis" is confusing and may have disastrous results. Ocular rosacea follows acne rosacea, and both are manifestations of the same disease and are

not due to riboflavin deficiency. Ocular rosacea is due to staphylococcal infection and must be treated by local antiseptic applications. I have repeatedly seen patients with severe ocular rosacea who did not improve until the local therapy was applied to the skin.<sup>26</sup>

Metabolic diseases of the liver are manifested by cutaneous discolorations ranging from jaundice to the irregular, yellow-brown pigmentation of the lower legs and yellowish, wedge-shaped conjunctival thickenings near the cornea. In many liver diseases, multiple functions being affected, more than one alteration in the appearance of the skin is observed.

Brunsting and Mason<sup>67</sup> report that bullous eruptions simulating epidermolysis bullosa, in which the exposed surfaces are sensitive to light, occur in association with porphyria and may represent the presenting symptoms of the disorder. Porphyria is recognized as a rare familial, metabolic fault in which abnormal kinds and amounts of porphyrins, especially uroporphyrin, are excreted in the urine and feces. Granted that there is a certain correlation between bullous eruptions, photosensitivity and porphyria in animals and in man, it is not proved that the production of the bullae on the exposed surfaces is due to the photodynamic action of porphyrins in the skin. Cutaneous signs of epidermolysis bullosa, melanosis and hypertrichosis were present in a case of porphyria, presumably of the tardive congenital type, occurring in a fifty-eight-year-old woman who had hepatic dysfunction and a history of alcoholism.<sup>67</sup>

The most striking and familiar skin affection associated with liver disease is jaundice. Pruritus is often associated with jaundice. It may be present without visible jaundice and may be the first indication of liver disease or, conversely, need not be present even though the icterus is marked. Biliary disease has also been reported to be the cause of 48 per cent of 200 cases of urticaria studied by Menagh,<sup>68</sup> who states that treatment of the biliary disease cured the urticaria in 60 per cent of cases.

A frequent finding in patients with liver disease is that of angiomas (telangiectasia or "spider angiomas") appearing on the face, neck, upper portion of the chest, shoulders and arms. Bean<sup>69</sup> asserts that there is an increase in the estrogen content of the blood, owing to inability of the liver to detoxify or otherwise cause an inert estrogen to be formed. Spider angiomas in the acute stage of infectious hepatitis have occasionally been described.<sup>70, 71</sup> In a clinical study of Navy patients at the Rockefeller Hospital, approximately 30 per cent developed spider angiomas during the acute stage of the disease.<sup>72</sup> New spider angiomas usually signified a poor prognosis when they developed after the acute stage of hepatitis.<sup>73</sup>

The vascular "spider" (naevus araneus, spider telangiectasia, spider angioma, stellate naevus and so forth) is a bright-red lesion characterized by a

central point from which fine, hairlike branches radiate for a distance of about 1 cm. Vascular spiders are seen in healthy persons, alcoholic patients, pregnant women and patients with liver disease and in avitaminosis. There is a hereditary tendency in which the lesions are found scattered over the skin and in the mucous membranes — that is, hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).

Williams and Snell<sup>74</sup> have suggested that the tendency to vascular spiders is transmitted as a dominant trait in some persons and as a recessive trait in others. The characteristic appears to be dominant in hereditary hemorrhagic telangiectasia, whereas it is probably recessive when there is no definite familial tendency. Vascular spiders frequently antedate the symptoms and signs of hepatic disease by as long as fifteen to twenty years. Patek et al.<sup>75</sup> reported them in 48 of 63 patients with hepatic cirrhosis. In a more extensive study of 368 cases of cirrhosis, Ratnoff and Patek<sup>76</sup> described vascular spiders in 15 per cent and telangiectasia in 17 per cent. The vascular spiders associated with pregnancy appear between the second and fifth months, usually increase in size and number until nearly term and may disappear abruptly a few days after delivery. Another group includes persons who are known to have or are suspected of having vitamin-deficiency diseases.

Palmar erythema may be hereditary or acquired, the latter being most frequently associated with liver disease, but occasionally with pregnancy and possibly with vitamin deficiencies. Ratnoff and Patek<sup>76</sup> reported this condition in 16 of 186 patients with cirrhosis of the liver, with a review of 20 cases of erythema palmare hereditarium, 9 presented by Walsh and Becker<sup>77</sup> and 11 collected from the literature. In 4 of their cases the condition appeared during pregnancy and was associated with the development of lesions similar to naevus araneus on the arms, face, neck and upper part of the chest. The complete clinical picture has not previously been described. Capillary studies usually show a dilatation of the venous side of the capillary loops and the superficial venous plexus.<sup>77</sup>

When estrogens were injected into patients with liver disease, angiomas appeared. Palmar erythema, especially thenar and hypothenar, was observed. Many chronic alcoholic patients show hypertrophy of the breasts and partial loss of pubic and axillary hair.

The skin manifestation due to faulty prothrombin and fibrinogen production consists of purpuric lesions and bleeding from the mucosal surfaces, especially the nose. The syndrome of pernicious anemia may result from inability of the liver to store the EMF as a result of disease. The skin manifestations may be pallor, glossitis, icterus and graying of the hair. The liver converts provitamin A to vitamin A, which it stores. In severe chronic disease of the liv-

er, vitamin A deficiency results, with xerophthalmia, a dry, harsh skin, follicular keratosis and acneiform eruptions. Yellow discoloration of the skin due to carotenemia may be secondary to liver diseases.

A skin disease and liver disease may coexist with neither the primary source in many cases, as in hemochromatosis, in which there is bronzing of the skin, loss of hair, a pigment cirrhosis of the liver and diabetes. At the same time, liver disease may occur secondary to skin disease. Miyake et al.<sup>78</sup> have shown that there is a so-called "G substance" in the skin of animals with a dermatosis that, when inoculated into rabbits, causes pathologic changes (chiefly cloudy swelling) in the liver, kidney and testis. Iwama<sup>79</sup> noted hepatic and renal insufficiency in cases of exfoliative erythroderma. One of his studies seems to offer evidence in favor of the liver as the cause of skin reactions. He concludes that there is a close relation between liver and skin disease.<sup>80</sup>

Altered metabolism of the liver may result in the formation of xanthomas. When one observes a yellow lesion or eruption on the skin, Melicow's<sup>81</sup> classification provides excellent data for a differential diagnosis. He states that xanthoma as a general term is inadequate and that the prefix "xanthic," which accurately characterizes the underlying condition, is more logical in most cases. According to his classification, the "pseudoxanthomas" or preferably the "xanthic granulomas" are manifestations of the reticuloendothelial response to destructive processes resulting in the accumulation of lipids and blood and are found in chronic inflammatory foci, neoplasm, possible selective response to an unknown irritant and when a metabolic disturbance is not demonstrable, such as xanthic granuloma palpebrarum (xanthelasma) or multiple xanthic granulomas, and possible response to repeated pounding, as in large arteries when cardiac hypertrophy and hypertension are present.<sup>82</sup> The xanthomatoses or preferably, the "xanthic lipidoses" are primary or secondary. Xanthic neoplasms included "xanthoma" or xanthic fibroma and xanthocarcinoma. Lesions simulating xanthic entities because of similarity in color comprise pseudoxanthoma elasticum, traumatic fat necrosis of breast and so forth, fibrohemangioma, hemorrhagic bursitis, hemorrhage in a lipoma, myxoma or fibromyxoma and melanotic tumors.

The classification of xanthomas has been confusing, probably owing to deficient knowledge of the normal physicochemistry of lipid metabolism. Various hormones in the pituitary and thyroid glands, the pancreas and the sex glands are closely linked with lipid metabolism. Disturbances of utilization of or deficiencies of various vitamins are also factors. Hypercholesterolemia and hyperlipemia may be seen in myxedema with lesions on the skin.

The exact etiology of the xanthomas is unknown, not all are associated with a hyperlipemia, and they may occur without liver disease. Montgomery,<sup>83</sup>



however, in a series of cases noted that cutaneous xanthomas (xanthoma tuberosum, xanthoma disseminatum and xanthelasma) are not infrequently seen in association with liver disease, especially in obstructive jaundice. There is usually a hyperlipemia with an increase in lecithin. Palmar lesions are frequent, often in association with lesions of the mucous membrane. Xanthomas often involute as the liver disease improves.

Eusterman and Montgomery<sup>84</sup> report the case of a woman of forty-eight who came to the Mayo Clinic in May, 1941, complaining of severe, refractory generalized intense pruritus, continuous aching pain and hyperesthesia, especially in both extremities, cutaneous yellow nodules, gastrointestinal disturbances, loss of weight and strength, yellowing discoloration of the skin and severe physical and nervous exhaustion. They stress the fact that cutaneous xanthomas and hyperlipemia occasionally occur in association with primary disease of the liver (so-called "xanthomatous biliary cirrhosis") and in association with hepatic disease that is secondary to obstruction of the common bile duct, especially as the result of postoperative stricture. In cases in which the hepatic disease is primary, the prognosis is generally unfavorable. It is more favorable in cases in which the underlying pathologic process is due to obstruction of the common bile duct.

Combes and Behrman<sup>85</sup> discuss xanthoma diabetorum and present a review of 181 cases from the literature. They suggest the more appropriate title "xanthoma eruptivum." The essential clinical features of the disease consist of the sudden appearance of multiple reddish-brown papules and nodules vaguely resembling erythema multiforme at their onset. The distribution is extensive, and the sites affected in particular are the extremities, the trunk and the mucosae. The lesions start as lentil-sized translucent nodules, sometimes with a small central blister. The diseases reported as extracellular cholesterosis and pseudodiabetic xanthoma are in all probability variants of xanthoma eruptivum.

To add to the confusion, a new entity—eosinophilic granuloma—has caught the interest of clinicians. In 1923 the histogenesis of eosinophilic granuloma was described as an unknown entity. The lesions have a dull erythematous appearance. They appear first as macules and develop into nodules or patches of firm elastic consistence varying in size from a millimeter to several centimeters. The accompanying blood eosinophil count ranges from 2 to 55 per cent, with an average of 20 per cent, lasting from two months to fifteen years. The name implies that there is an infiltration of polynuclear and mononuclear eosinophils in the dermis, which may extend into the subcutaneous tissue.<sup>86</sup>

Johnson and Zonderman<sup>87</sup> report a case involving the frontal bone, with recovery following surgery and x-ray therapy. Jaffe and Lichtenstein<sup>88</sup> define eosinophilic granuloma as a "condition affecting

one, several or many bones, but apparently limited to the skeleton, and representing the mildest clinical expression of the peculiar inflammatory histiocytosis also underlying Letterer-Siwe disease and Schüller-Christian disease." Green and Farber,<sup>89</sup> Mallory,<sup>90</sup> Jaffe and Lichtenstein<sup>88</sup> and others have shown that the underlying lesion of this disease is related to the lesions of Schüller-Christian's disease and those of Letterer-Siwe's disease, which represents the gravest (eosinophilic granuloma representing the mildest) expression of the same basic pathologic process, which appears to have a predilection for the hemopoietic system. When this "peculiar inflammatory histiocytosis" manifests itself in infancy in its severe and often fatal form—characterized clinically by fever, purpuric skin rash, rapidly progressive hypochromic anemia, enlargement of the spleen, liver and lymph nodes and destructive bone lesions—it is classified as Letterer-Siwe's disease (aleukemic reticulosis, nonlipoidal histiocytosis). In its more chronic and less severe form, occurring in childhood and early adult life, after the lesions of the soft tissues and the bones have undergone lipogranulomatous changes, and especially—although not characteristically—when the Christian triad of symptoms (calvarial defects, exophthalmos and diabetes insipidus) has developed, the disease is labeled Schüller-Christian's disease (lipogranulomatosis). Roentgenographically the lesions appear as radiolucent areas varying in size. In the skull they tend to be round and sharply defined and have a punched-out appearance.

Nanta and Gadrat were the first to use the full term "eosinophilic granuloma of the skin" in 1937. This term was applied to bone by Finzi in 1939. The syphiloid of cats was described as "la syphiloïde du chat (granulome eosinophilique)" by Henry and Bory in 1937. On the basis that Nanta and Gadrat have priority, the characteristics in their case should serve as the type for eosinophilic granuloma of the skin. The earlier reports of the disease indicate that the authors arrived rather promptly at the conclusion that it was not a clinical or etiologic entity. Therefore, the term can be used with the utmost latitude in any dermatosis with extreme eosinophilia in the tissues. In any event, attention should be focused on newer factors in the life of the population that might bear an influence on its tissue, especially the hemopoietic ones. The sulfonamides, barbiturates, aminopyrin and ethyl lead must be thought of when the clinical history is being elicited. In Weidman's<sup>41</sup> cases only two opportunities were supplied for testing for the presence of fat in the skin. Lever,<sup>91</sup> alone, raised this subject, he found new lipid-laden histiocytes and foam cells in his sections. In Weidman's sections there was no evidence of such disintegration.

Troxler and Niemetz<sup>92</sup> report a case of generalized xanthomatosis with involvement of bone, lungs and cerebrum. The unusual complication of bilateral

spontaneous pneumothorax occurred in this case. In the discussion they mention Hand-Schüller-Christian's disease as being considered as cranio-hypophyseal localization of lipid granulomatosis. They quote Green and Farber<sup>91</sup> in concluding that eosinophilic or solitary granuloma of the bone is one form of generalized xanthomatosis and not a new disease entity. These authors also describe Letterer-Siwe's disease or reticuloendotheliosis as the same pathologic process seen in Hand-Schüller-Christian's disease. Wherever there is reticuloendothelium there can be lipid granulomatosis. Thus, the clinical symptoms produced depend on the tissues involved and the degree of involvement.

Several interesting papers reporting eosinophilic granuloma with cutaneous manifestations have appeared in the dermatologic literature.<sup>91, 92, 93</sup> Just as I had decided on the cutaneous picture of eosinophilic granuloma, I saw a case of Thannhauser's presenting yellow, xanthomatous plaques on the eyelids and a yellowish, saber-blade type of patch extending from the hairy margin to the vertex of the scalp, with multiple small, dark-brown macules on the extremities, with symptoms of cerebral involvement and with a positive biopsy from the femur.

Some believe that eosinophilic granuloma is merely a late stage of a xanthomatous process. Others regard the lipid factor as a secondary development due to the infiltration of the lipid material into the granulomatous tissue. Apparently there are several symptom complexes with individual cases showing characteristics of more than one group. These syndromes include xanthomatosis of the skin and mucous membranes, Hand-Schüller-Christian disease, Niemann-Pick disease, Tay-Sachs disease and Gaucher's disease. A hypercholesteremia may or may not be present. Xanthomatous nodules and plaques may appear in almost any tissue, occasionally with enlargement of the spleen, liver and lymph nodes. Therefore, when a physician sees a cutaneous yellow lesion he should consider it a cutaneous manifestation of a general disturbance until he proves otherwise. Xanthomas secondary to general pathologic conditions such as diabetes mellitus and jaundice tend to disappear with proper systemic therapy. Skin lesions, however, may be independent of other disease.

Niemann-Pick<sup>94</sup> disease, or acute idiopathic lipidosis, is a rare congenital familial disorder of lipid metabolism in which the blood and tissues become overloaded with lipids, chiefly the phosphatide lecithin. The disorder begins in infancy, usually in the first six months of life and nearly always before the age of one year. Pfändler<sup>95</sup> reviewed observations on 14 members of a family in which 2 brothers died with Niemann-Pick disease at the ages of twenty-nine and thirty-three years, respectively. These cases demonstrate that this disease is exclusively a disease of infants and young chil-

A genealogical tree of the family illustrates diagrammatically the various forms in which Niemann-Pick disease became manifest. Pfändler regards the latent forms as possibly more frequent than is generally believed.

Gaucher's disease, the second related disease, is a rare familial constitutional disorder of metabolism. It was first described by Gaucher<sup>97</sup> in 1882. The two types — the chronic and the rare acute form — are characterized pathologically by an enormously hypertrophied spleen and an enlarged liver, each of which shows on microscopical examination an infiltration of cells peculiar to the condition. These distinctive cells vary in diameter from 20 to 40 microns, stain palely with eosin and are usually oval or polygonal. The typical eruption of Gaucher's disease is a brownish-yellow pigmentation or bronzing of the skin, more pronounced and of a deeper hue on the face, neck, forearms and hands.<sup>98-100</sup> The other common lesions of the skin are of the hemorrhagic type — that is, petechiae, ecchymoses and hemorrhagic furuncles.<sup>101, 102</sup> A diagnosis of Gaucher's disease is suggested by an enormous abdomen, bronzing of the skin and a hemorrhagic diathesis. The presence of Gaucher's cells in the biopsy material from a peripheral lymph node or a splenic puncture is positive proof of the diagnosis.<sup>103</sup>

Acute pancreatitis is accompanied by a pallor, cyanosis or lividity of the face and a cold clammy skin. Intestinal infestations may announce their presence by pruritic symptoms and lesions varying from a perianal eczema to the giant wheal. Persistent diarrhea with dermatitis and some mental change complete the syndrome of pellagra.

#### Blood

Osler was one of the first to recognize the syndrome called polycythemia vera, splenomegaly, cyanosis (erythrosis) and plethora.<sup>104</sup> Strickler<sup>105</sup> states that there are two frequent cutaneous manifestations of polycythemia vera: a purplish redness of the gums due to a highly reduced oxyhemoglobin content of the blood and a papular, pruritic, urticarial eruption with surmounting vesicles or pustules occurring in crops, which later become bloody crusts. This has been called *acne urticata polycythemia*.

Klauder<sup>106</sup> previously described this entity in a patient who had typical signs and symptoms consisting of headache, hypertension, albuminuria, hepatosplenomegaly, vasomotor instability, flushing, dermatographism, a high blood uric acid and occasional ecchymosis. Marsh<sup>107</sup> distinguishes between the cyanosis seen in anoxic diseases and the erythrosis present in this entity, in which there is often an increased oxygen content. Brown and Griffin<sup>108</sup> believe that cutaneous lesions may be due to multiple thrombi and conclude that the erythrosis is due to peripheral vessel engorgement.

Anemia has various skin manifestations — the wax, delicate skin of the victim of pernicious

anemia, the green-yellow tint of the sufferer from hypochromic anemia and the smoothness and shiny appearance of the tongue seen in dysphagic old women with the Plummer-Vinson syndrome<sup>109</sup> Spoon nails are also noted in this disease<sup>110</sup>

Ulcers of the legs are observed in sickle-cell anemia, exclusively in Negroes<sup>111, 112</sup>

Infectious lymphadenosis may present a roseolar eruption resembling syphilis, and an accompanying positive serologic reaction may deceive the unwary physician Dameshek and Grassi<sup>113</sup> reported the case of a young woman with severe purpura hemorrhagica accompanied by generalized lymphadenopathy and a marked lymphocytosis Although the clinical picture resembled that of acute lymphatic leukemia, the character of the lymphocytes suggested infectious mononucleosis, this was confirmed by a strongly positive heterophil-antibody agglutination When the bleeding became uncontrollable, splenectomy was performed and resulted in prompt recovery

Urticaria may be present in acute infectious lymphocytosis<sup>114</sup> Eosinophilia may be found in conjunction with diseases of the skin Kirk<sup>115</sup> divides the causes of eosinophilia into five classes intestinal parasites — nematodes and some cystodes, blood diseases — eosinophilic leukemia and Hodgkin's disease, skin diseases — dermatitis herpetiformis and pemphigus, allergic diseases — asthma, eczema and hay fever, and miscellaneous diseases — periarteritis nodosa, trichinosis and Loeffler's syndrome and those occurring after the ingestion of raw liver A significant rise in the eosinophils is present in urticaria, the neurodermatoses, pemphigus, erythema multiforme bullosum, dermatitis herpetiformis, hydroa, herpes iris, herpes gestationes and rarely in psoriasis<sup>116</sup>

The eosinophil has been called a histamine scavenger I have seen a 97 per cent eosinophil count with a white-cell count of over 65,000 in a case of generalized dermatitis from mercury The blood became normal with clearing of the rash Perhaps further study of eosinophilia will reveal the etiologic factor in some bullous diseases

Purpura has been reported as resulting from many different factors — heredity, avitaminosis, allergy, anaphylaxis, infection, drugs and physical anomalies As knowledge of the relation of drugs, infection and certain other conditions to thrombocytopenic purpura increases, the disease is less often described as idiopathic Infection as an exciting cause of purpura is mentioned in most discussions of the etiology of thrombocytopenia The etiologic importance of localized infection in the throat has been emphasized by many writers Thrombocytopenic purpura following angina was considered sufficiently rare to warrant report of a fatal case<sup>116</sup> Frey<sup>117</sup> and Berg<sup>117</sup> reported the first case in which the initiation of a vaccine followed by

angioneurotic edema involving parts of the body far from the site of the injection Hampton<sup>118</sup> states that food allergy caused 2 cases of purpura of the Henoch type

Rucks and Hobson<sup>119</sup> reiterate that purpura fulminans is with few exceptions found in children owing to a fulminating blood-stream infection They have reviewed 101 cases

It is stated that purpura following the use of drugs such as arsenic, sulfonamides, coal-tar derivatives and gold is fairly frequent<sup>120-122</sup> Several excellent reviews on purpura have recently been published<sup>123-127</sup>

In discussing a rare fatal case of Henoch-Schönlein's purpura, Moore<sup>128</sup> states that fibrosis of the liver, seen in this case, is not found in lupus erythematosus or periarteritis nodosa, which others considered in differential diagnoses

The detection of the causative factor of a purpuric eruption necessitates careful history taking, physical examination and laboratory studies Very few cases can be diagnosed from observation, and the services of an expert hematologist are usually required

Although in the experience of some clinicians leukemia cutis is rare,<sup>129</sup> in the practice of the dermatologist it is frequent enough to keep the possibility of its occurrence ever present in his mind A persistent pruritus always demands a thorough blood study in the young or the old. An acute ulcerative stomatitis may be the precursor of monocytic leukemia, and an acute exfoliating dermatitis may precede by months a change in the blood picture I have seen so many varied types of eruption accompanying the leukemias that I hesitate to name any single eruption as being specific, for even in the tumor stage the lymphomas may all resemble one another histologically and repeated biopsies are often necessary for the final diagnosis The nonspecific lesions may be wheals, extravasation of the blood, papules, vesicles (single or grouped), bullae or ulcerations Herpes zoster is frequently associated with the lymphatic group Within two months I saw a patient with a generalized herpes zoster and another with an exanthema indistinguishable from varicella. Specific lesions due to infiltration of the leukemic process in the skin are those producing erythroderma, nodules and tumors, the last may break down into ulcerations Nodules appear most frequently on the skin Many excellent reviews have been published on the oral and cutaneous manifestations of the leukemias<sup>130-146</sup>

Jackson and Parker<sup>146</sup> state that the skin lesions of Hodgkin's granuloma are often encountered Marked excoriations due to severe pruritus of the skin are perhaps the most frequent lesions Generalized or, more rarely, localized pigmentation occurs aside from that due to radiation therapy Herpes zoster, not infrequently of a hemorrhagic type and often leaving behind it an indurated scar, is not unusual The more specific lesions are generally

nodular or ulcerated and may exist for a long time prior to unequivocal evidence of the disease elsewhere.<sup>116</sup> Generalized exfoliating dermatitis has been reported, Jackson and Parker<sup>117</sup> saw 1 patient with this complication. In the past year I have treated 2 patients with a generalized dermatitis due to Hodgkin's disease.

The clinician should bear in mind that any chronic skin disease, whether it starts as a simple scaly eruption, such as parapsoriasis or psoriasis, or a vesicular eruption, such as chronic eczema, may eventually terminate as a fatal lymphoma. Hodgkin's disease should always be suspected in a persistent dermatitis exfoliativa, even if there is no visible adenopathy. I have seen more cases in the last few years than in all my previous years of practice. A well known hematologist remarked that the sulfonamides may be a factor, but I have failed to find a history of the ingestion of this drug except in the case of erythroderma suspected of being Hodgkin's disease. Other authors have reported eruptions varying from ichthyosis to ulceration.<sup>118-122</sup>

(To be concluded)

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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### CASE 33501

#### PRESENTATION OF CASE

A sixty-seven-year-old man entered the hospital with the chief complaint of food sticking in his throat.

For four months he had had difficulty swallowing solid food. If he swallowed a large particle, it stuck and produced a burning sensation in the lower sub-sternal region, and no more food could pass for a while. Induced vomiting relieved the block. Liquids and soft solids were easily swallowed. There had been no weight loss, pain, cough or hematemesis. He had been slightly hoarse for three weeks.

X-ray studies and esophagoscopy at another hospital had demonstrated a lesion of the lower esophagus, which was not further described.

Physical examination disclosed a Grade II apical systolic murmur and a slightly enlarged prostate.

The temperature was 98°F, the pulse 60, and the respirations 17. The blood pressure was 160 systolic, 70 diastolic.

Examination of the blood revealed a hemoglobin of 15.1 gm and a white-cell count of 8000. The urine was normal, with a specific gravity of 1.027. The total protein was 6.3 gm and the nonprotein nitrogen 29 mg per 100 cc. An electrocardiogram showed changes consistent with coronary-heart disease.

X-ray examination demonstrated an essentially normal chest. A gastrointestinal series showed a 2-cm area of narrowing in the distal portion of the esophagus. No ulceration was seen. No tumor mass was visible. There was herniation of a portion of the stomach through the diaphragm. The films were otherwise negative.

An esophagoscopy was not performed. On the eighth hospital day an operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR EDWARD B. BENEDICT. Difficulty in swallowing is a very serious symptom and may be produced in a number of conditions, including benign and malignant tumor, benign stricture, cardiospasm, peptic ulcer of the esophagus, esophagitis, chemical burn and foreign body.

At the age of sixty-seven years, with a four-month history of dysphagia beginning with difficulty in swallowing solid food, the presumptive diagnosis is carcinoma of the esophagus until proved otherwise. The fact that food stuck and produced a burning sensation in the lower sub-sternal region indicates that the lesion was in the lower esophagus, and the burning sensation points a little more toward an inflammatory process such as ulcer or esophagitis with benign stricture than to a tumor or to cardiospasm. The relief of the obstruction by induced vomiting does not help very much in the differential diagnosis. That liquids and soft solids were easily swallowed merely indicates that the obstruction was not complete and does not aid very much in the differentiation of a benign stricture from a carcinoma. One would expect, however, that an annular carcinoma of four months' duration would have produced some difficulty in swallowing soft solids and would probably have resulted in some loss of weight. The absence of pain is definitely against a diagnosis of peptic ulcer of the esophagus and somewhat against that of acute esophagitis. Sub-sternal burning, however, is closely akin to pain. A cough in esophageal disease is usually secondary to rather complete esophageal obstruction with

spillage of food material into the trachea. This may occur in advanced cardiospasm or the late stages of carcinoma. There is little in the history to suggest cardiospasm, which is usually a disease of younger persons and occurs intermittently, frequently with emotional factors prominent in precipitating the attacks. The absence of hematemesis is not particularly helpful, because even in the presence of large ulcers or cancers of the esophagus, bleeding may not be a prominent symptom, and what bleeding does occur may be in the form of melena.

The hoarseness of three weeks' duration suggests the possibility of a malignant lesion with pressure on the recurrent laryngeal nerve and paralysis of a vocal cord. The hoarseness, however, may have been an incidental finding and not related to the esophageal disease, but due to a laryngitis.

There is nothing in the history to suggest a chemical burn such as the ingestion of lye, nor is there any history of foreign body.

Physical examination and laboratory studies are not particularly helpful, but a normal hemoglobin suggests the absence of cancer and the absence of a bleeding lesion.

We are told by the radiologist that there is a hiatus hernia and 2-cm. area of narrowing in the distal esophagus, with no visible ulceration or tumor mass.

The differential diagnosis from the above discussion seems to boil down to a carcinoma of the distal esophagus and a benign stricture with or without peptic ulceration. The fact that no ulceration was seen does not mean that none was present, for small ulcers of the esophagus are notoriously hard to demonstrate by the x-ray. The absence of a tumor mass is somewhat against the diagnosis of carcinoma. We are not told whether the area of narrowing is irregular or whether the margins of it are smooth. Obviously, a smooth narrowing would be more suggestive of a benign stricture, whereas a nodular narrowing would suggest cancer. Smooth narrowings, however, should always be viewed with some suspicion, since there may be a relatively smooth annular carcinoma simulating a benign stricture.

On the whole, I vote for benign stricture of the lower end of the esophagus associated with esophagitis for the following reasons: burning sensation in the lower substernal region, no weight loss, normal hemoglobin, no evidence of nodularity by x-ray examination and the presence of a hiatus hernia as described on x-ray study.

It has been my experience that benign strictures of the esophagus quite frequently occur in association with hiatus hernia, duodenal ulcer or esophageal ulcer. In a study of 44 cases I found that the disease was relatively infrequent in women, and that it occurred usually in men over fifty years old. In the series reported the benign stricture was associated with hiatus hernia in 17 cases, with duodenal

ulcer in 15 and with esophageal ulcer in 8.\* All the patients had some esophagitis.

In the case presented herewith no esophagoscopy was performed, presumably because the surgeon planned to do a resection of the lower end of the esophagus, regardless of whether he was dealing with a benign stricture or with a carcinoma. This method of treating a benign stricture of the lower end of the esophagus is a debatable point, since the results of esophagoscopy and bouginage, a previously swallowed thread being used as a guide, are usually satisfactory. In my opinion esophagoscopy should be done in all these cases, and adequate biopsy obtained from the lumen of the stricture, to make absolutely positive that one is not dealing with carcinoma. Bougies may then be passed at regular intervals, and a major operation thus avoided. It must be remembered that patients with esophagitis and benign stricture may have a normal acidity, and that the usual operation of esophageal resection with esophagogastric anastomosis leaves the lower end of the esophagus even more vulnerable than before to the action of the acid gastric juice, thus leading to the possibility of further esophagitis with or without esophageal ulcer. The time for major surgery in a patient of this sort, sixty-seven years old, is, it seems to me, after conservative measures have failed.

Dr. Robbins, will you please help us with the x-ray interpretations?

DR. LAURENCE L. ROBBINS: Although I did not fluoroscope the patient, the films show a small hiatus hernia and approximately 2 cm. above the cardia of the stomach there appears to be a crater about 1 cm. in diameter. There is no evidence of a shelf, and no mass is seen either extrinsically or protruding into the lumen.

The remainder of the stomach and the chest show no evidence of tumor.

DR. BENEDICT: Dr. Robbins believes that there is probably an esophageal ulcer. The radiologist who did the fluoroscopy saw no ulceration. Naturally, it is impossible to be sure. My diagnoses are hiatus hernia, esophagitis, benign stricture of the esophagus and question of esophageal ulcer.

DR. RICHARD H. SWEET: One of the principal reasons for operating on this man was the fact that an esophagoscopy had been performed at another hospital by a competent endoscopist and that a biopsy specimen obtained at that examination had been reported as epidermoid carcinoma by the pathologist. Obviously, the history was not that of carcinoma because of its long duration. Also, the patient was actually able to swallow considerable food at the time we saw him even though he had had his trouble for a long time.

An exploration of the chest was therefore carried out, and at operation, although it was not ab-

\* Benedict, E. B. Benign stricture of esophagus. *Gastroenterology* 6: 328, 1946.

solutely certain that we were dealing with a benign lesion, it seemed more than likely that it was an inflammatory stricture with ulceration rather than carcinoma, although a small carcinoma superimposed on an ulceration in that region could exist without my being able to determine its presence by palpation and inspection alone. I have actually had that experience in just such a case.

This brings up an important point, which I believe should be mentioned lesions of this sort, in my opinion, should be regarded with as much suspicion as the prepyloric ulcers of the stomach because as experience is accumulated with them, I am willing to predict that there will appear to be a correlation between the pre-existence of such a lesion and some cases of carcinoma, of about the same magnitude as that with prepyloric ulcer.

I therefore proceeded with a resection and an esophagogastric anastomosis.

#### CLINICAL DIAGNOSIS

Carcinoma of esophagus, benign stricture with ulceration?

#### DR BENEDICT'S DIAGNOSES

Benign stricture of esophagus, with (?) ulcer  
Esophagitis  
Hiatus hernia

#### ANATOMICAL DIAGNOSES

Peptic ulcer of esophagus  
Acute and chronic esophagitis

#### PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN The specimen received in the laboratory showed a shallow ulcer 2 cm. in diameter whose margins were irregular but well defined and not indurated. Microscopically, the base of the ulcer was covered with a fibrinoid membrane characteristic of peptic ulceration. There was no evidence of carcinoma. The surrounding esophageal mucosa and muscularis were moderately inflamed.

DR. SWEET The patient made an exceedingly rapid and favorable convalescence. At the time he left the hospital he was eating a liberal solid diet with much more comfort than he had for years.

### CASE 33502

#### PRESENTATION OF CASE

*First admission.* A sixty-nine-year-old physician was admitted to the hospital complaining of slowing of the urinary stream and nocturia.

For several years the patient had suffered from increasingly severe nocturia, frequency and difficulty in starting the urinary stream. He had had diabetes for several years and was satisfactorily

controlled on 8 units of protamine-zinc insulin daily.

Physical examination revealed a healthy-appearing, unusually well preserved man. The heart was of normal size, and a soft systolic murmur was heard at the apex. The abdomen was normal. Rectal examination disclosed a smooth, symmetrically enlarged prostate.

The temperature, pulse and respirations were normal, the blood pressure was 165 systolic, 90 diastolic.

Examination of the blood revealed a hemoglobin of 13.8 gm. and a white-cell count of 6100. The urine had a specific gravity of 1.020 and gave a + test for albumin and a negative test for sugar. The urinary sediment contained 10 red cells, 150 white cells and numerous bacteria per high-power field. The nonprotein nitrogen of the blood was 122 mg. per 100 cc. A blood Hinton test was negative.

X-ray studies showed normal kidney outlines, the left kidney being somewhat low. The ureters were not dilated. No unusual soft-tissue mass was present. A large amount of mottled calcification was seen in the region of the prostate. The walls of the pelvic vessels were calcified.

On the fourth hospital day cystoscopy showed marked trabeculation of the bladder but was otherwise not remarkable. A perineal prostatectomy with removal of 20 gm. of tissue was performed. Pathological examination revealed hyperplasia and chronic prostatitis.

Recovery was uneventful, and the patient was discharged on the nineteenth hospital day.

*Second admission* (six months later). The patient had felt well for the first three months following discharge, but then noted indefinite suprapubic discomfort and pain. The pain gradually became severer and seemed to be localized in the right lower quadrant. In addition he had a slight afternoon fever. He was nauseated once, but there was no vomiting or change in bowel habit.

During the week prior to admission penicillin was administered without much effect. On the day before re-entry the pain became so severe that three injections of morphine were required for relief. The pain during this attack radiated into the groins.

The temperature was 100.2°F, the pulse 115, and the respirations 20.

There was slight tenderness over McBurney's point, without spasm. No masses were palpable, and rectal examination was negative. The palpable remnant of the prostate was small and symmetrical, without nodules or tenderness. There was no costovertebral-angle tenderness.

Examination of the blood disclosed a hemoglobin of 12.6 gm. and a white-cell count of 18,100. Urinalysis showed a specific gravity of 1.028, a ++ test for albumin and a yellow-brown test for sugar. Ureteral catheter specimens showed 45 to 75 red cells and 1 white cell per high-power field. The non-



protein nitrogen was 29 mg, and the fasting blood sugar 380 mg per 100 cc

Retrograde pyelograms showed normal kidney shadows, and the pelves, calyces and ureters were not abnormal so far as visualized. X-ray films of the chest disclosed a few linear streaks on the lower right and middle portions of the chest. A barium enema revealed numerous diverticula in the sigmoid colon. The appendix did not fill, but on the following day a linear streak of barium consistent with the appendix was seen in the right lower quadrant. A cystogram showed several diverticula of the bladder.

The patient's condition during the first week in the hospital remained unchanged. The diabetes was brought under satisfactory control with insulin. The tenderness in the right lower quadrant persisted, and there was a daily rise in temperature to 101 and 102°F. The tenderness was sometimes prominent along the brim of the pelvis and above the pubis, as well as in the right lower quadrant just medial to and below the anterior superior spine of the ilium. No tenderness or masses were found on further rectal examination. On the eleventh hospital day one observer felt a tender mass in the right lower quadrant, with pain radiating to the scrotum on pressure.

An operation was performed.

#### DIFFERENTIAL DIAGNOSIS

DR F A SIMEONE This sixty-nine-year-old man, who had an operation for what was presumably an inflammatory mass, because the mass was tender, had fever, leukocytosis and an increase in the pulse rate. I believe that the problem is to decide the nature of this inflammatory mass.

In reviewing the history of the previous admission we come to the conclusion that this was an ordinary case of benign hypertrophy of the prostate gland and that the perineal prostatectomy had been satisfactory. The patient was relieved and went home after nineteen days. The only unusual point is that he had a nonprotein nitrogen of 122 mg on that admission. The urine was infected, as manifested by the 150 white cells per high-power field. This, together with back pressure, must have led to a certain degree of renal insufficiency. The infection subsided quickly, for the surgeon considered the patient ready for operation on the fourth day of hospitalization. There were no complications after operation and no evidence that a malignant tumor in the gland was missed. He was relieved after this operation for a period of three months, during the second three-month period, however, he began to get into some kind of trouble that was unrelenting and progressive to a point where operation became necessary. He first noted indefinite suprapubic discomfort and pain, — rather nondescript symptoms, which could be accounted for by a number of different conditions, — but the pain gradually became

progressively severer and began to be localized in the right lower quadrant. In addition, he had fever, suggesting that this was probably an inflammatory process. One immediately thinks of appendicitis, — pain in the right lower quadrant is acute appendicitis until proved otherwise, — but this was certainly a strange course for appendicitis to follow. The patient had symptoms for three months. The pain radiated into the right groin. One wonders about the explanation for that. Could this pain in the right lower quadrant have been the pain of, let us say, acute inflammation of the seminal vesicles? Sometimes that pain does radiate into the right lower quadrant and into the groin, but the rectal examination was described as negative. The tenderness in McBurney's point was localized, but without spasm, and no masses were felt over a period of three months. Acute appendicitis of that duration is extremely unlikely. We have the help of the definite statement that the remnant of the prostate was certainly not at fault at that time. There was no costovertebral-angle tenderness to suggest that this was a referred pain from the kidney and upper ureter. The urinalysis was abnormal, of course, in that it showed glycosuria and a ++ test for albumin. We know that the patient had diabetes. Perhaps, with this added infection, the diabetes had got somewhat out of control.

It would be interesting to know for the differential diagnosis what the cellular content of the urine was. We know that the urine from the kidneys was normal. One might expect 45 to 75 red cells per high-power field from catheterization of the ureters and kidneys, but it would be interesting to know how many white cells there were in the bladder urine.

DR GEORGE G SMITH I am sure that there were a good many white cells. There was about 20 ounces of residual urine.

DR SIMEONE It was grossly infected urine?

DR SMITH Yes, slightly cloudy.

DR SIMEONE We have further evidence from the x-ray studies, and I shall ask Dr Wyman to present the films.

DR STANLEY M WYMAN At the time of the first admission the intravenous pyelogram showed a rather diminished function of the kidneys. The left kidney can be outlined lying somewhat low with normal contour. The right kidney is poorly seen but not remarkable. The dye filling is inadequate in both kidneys. There is trabeculation of the bladder and a diverticulum on the left, and a larger, broader diverticulum on the right. There are some changes in the bone structure of the pelvis consistent with Paget's disease. There is calcification in the region of the prostate, which appears to be large. The second film is that of a retrograde pyelogram and shows good filling of the right kidney, with rather faint filling of the left. No abnormality is demonstrated in either kidney. The ureters appear normal.

Dr. SIMEONE Is the irregularity at this point explained on the basis of trabeculation, or can it be a different kind of filling defect?

Dr. WYMAN I think that the irregularity on the right border is probably a diverticulum. I cannot demonstrate it well in these films. We have later films of the bladder that show a definite diverticulum on the left and probably one on the right. At least one lies more on the superior border. This is the shadow of the appendix. The barium enema showed diverticula throughout the sigmoid but no other gross lesion.

Dr. SIMEONE Are these shadows all in the appendix? Does it curve all the way around, or is this shadow in tissue other than the appendix?

Dr. WYMAN I believe that it curls as you suggest. I cannot be sure, however. I think that the appendix lies over the sacroiliac joint.

Dr. SIMEONE It is mentioned in the history that there were shadows in the lung field. I assumed that these were consistent with old atelectasis instead of malignant lesions.

Dr. WYMAN The lung fields show about three linear shadows, which can be focal atelectasis or possibly old infarcts. There is some prominence of the left cardiac border in the region where the pulmonary artery is expected to lie, which probably represents prominence of that artery. I see no evidence of destruction of the ribs or metastatic nodules in the chest.

Dr. SIMEONE The patient's condition changed while he was on the ward, and a palpable mass in the right lower quadrant was felt by at least one observer. It would be interesting to know whether this mass was felt to extend into the pelvis or whether the outlines could be clearly defined and localized in the right lower quadrant. There is probably no mention of that in the record. This mass was not felt by rectal examination, suggesting that it was probably out of the true pelvis.

I believe that with this information we might embark on a differential diagnosis of this inflammatory mass. First of all, could this mass have been entirely independent of the genitourinary tract? We have the information that the patient had diverticula in the sigmoid, but there was no evidence of diverticulitis. Demonstrable diverticula, of course, are fairly common in the general population, but they seldom produce trouble. Perhaps 1 out of 10 cases may develop diverticulitis and cause trouble for the patient. An inflammatory mass may result from diverticulitis, but one would expect it to be on the left side and not on the right, although if the sigmoid was very mobile it might appear on the right side. There is no evidence of such a position of the sigmoid in the examination by barium enema.

Could this have been a late result of acute appendicitis? This was certainly not the usual case of acute appendicitis. However, an acute inflammatory lesion in the appendix may be dependent on

some other more chronic lesion in it. For example, the patient could have had a carcinoma in the appendix, with inflammatory changes about it, increasing in degree until a palpable mass was felt, or he may have had a carcinoid of the appendix. Both these lesions, particularly the former, are extremely rare but might explain this case. The radiation of pain was a little unusual unless we assume that the appendix was lying in the pelvis. The filling of the appendix by means of barium. I consider evidence against its involvement in this process, although filling of the appendix has been observed in acute appendicitis.

Could the patient have had a diverticulum of the cecum? I think that the chances for that are remote, and I shall dismiss it for lack of x-ray evidence. There is no apparent intrinsic lesion of the cecum that might give rise to this inflammatory mass in the right lower quadrant.

Can we relate this mass to the disease of the genitourinary tract? In favor of that supposition is the fact that the patient had trouble with the genitourinary tract, and it would be satisfying to explain this lesion on the same basis. In favor, also, of connecting this disease with the genitourinary tract is the fact that diverticula were demonstrated in the bladder by x-ray study. Were they seen by cystoscopy?

Dr. SMITH Yes, they were.

Dr. SIMEONE It is possible that one of the complications of diverticula of the bladder developed, particularly if there was evidence of persistent infection in the bladder urine. The complications of diverticula are well known. Frequently, stones develop in bladder diverticula. Less commonly, tumors develop in bladder diverticula. Finally, such diverticula may develop peridiverticulitis, with extension into the extraperitoneal pelvic tissues and sometimes actual rupture into the peritoneal cavity, leading to general peritonitis. Against the supposition that this lesion was connected with the disease of the bladder is the fact that no tenderness was elicited by rectum. If this had been an extension of inflammation from the bladder diverticulitis one would expect to feel some tenderness in the right side on the pelvic floor. Taking these possibilities together, the evidence is a little in favor of linking the present lesion with the genitourinary tract. The evidence is against the possibility of a disease referable to the gastrointestinal tract, and it is entirely possible that the patient developed a peridiverticulitis about this one diverticulum, with extension into the right lower quadrant leading to the mass that was palpated by the observer.

The next question that one might consider is whether this was an otherwise uncomplicated form of bladder diverticulitis or a tumor within the diverticulum that had grown and penetrated its walls. That is certainly a possibility, although we have no evidence for it except as a good guess. I

shall therefore make a preoperative diagnosis of right-lower-quadrant abscess due to extension of a peridiverticulitis of the bladder with a question of tumor within it

DR BRIANT L DECKER I saw this man several times. As I remember the history I thought that it was of shorter duration. He had severe pain associated with nausea of about five weeks' duration, although it is perfectly true that he may have had some discomfort before that. I thought that he had an appendiceal abscess. Just before he came to the hospital he was x-rayed outside, and the appendix was visualized. The note was made that the tip of the appendix was fixed and tender. I also thought that he was given streptomycin while he was in the hospital, and I think that the temperature came down to normal while he was on the streptomycin.

DR SMITH The first mention of the suprapubic discomfort was about three months before the patient died. I had seen him, and when I came back five weeks later the tenderness had increased. I was extremely puzzled why he had this fever and tenderness. I was the one who felt the mass, and I would say that it was small, about 2 or 3 cm in diameter, just to the medial side of McBurney's point. There was nothing felt in the pelvis by bimanual examination. My next guess was that he had an infection of the iliac and aortic lymph nodes that was forming an abscess. He was seen by a surgical consultant, who first did not think that there was any indication for exploration but later did explore him. I think that if Ellery Queen were here he would get a lead from those x-ray films.

DR TRACY B MALLORY Have you anything further to say, Dr Wyman?

DR WYMAN I remember the answer and therefore cannot say anything.

#### CLINICAL DIAGNOSIS

Ruptured aortic aneurysm

#### DR SIMEONE'S DIAGNOSIS

Abscess of right lower quadrant from extension of peridiverticulitis of bladder

#### ANATOMICAL DIAGNOSES

*Ruptured arteriosclerotic aneurysm of right iliac artery, with retroperitoneal hematoma*

Arteriosclerosis, generalized

Diverticulum of bladder

Diverticulosis of sigmoid

#### PATHOLOGICAL DISCUSSION

DR MALLORY This man was explored by Dr Sweet, who found an aneurysm at the junction of the iliac artery and the aorta. Two days later the aneurysm suddenly burst, and the patient went into profound shock and died within a few hours of the episode.

At autopsy we found a massive retroperitoneal hematoma, which had dissected into the mesentery of the cecum and ascending colon and also had dissected beneath the parietal peritoneum around the lateral wall of the abdomen. The total hematoma was estimated to contain something in excess of 2 liters of blood. It seems probable that there had been minor leakage before the terminal episode to account for the attacks of acute pain.

The other findings were all historic landmarks and had nothing to do with the symptomatology. There was a slightly hypertrophied heart to go with the mild hypertension. There was a rather severe generalized arteriosclerosis but no dilatation of the aorta itself. The aneurysm was sharply limited to the right iliac artery. The sigmoid was full of diverticula, none of which appeared inflamed. The bladder also contained numerous diverticula that were not inflamed. There was a remnant of prostatic tissue left from the perineal prostatectomy. Have you anything further to add, Dr Smith?

DR SMITH In the x-ray film the right ureter takes a peculiar course as it comes down over the brim of the pelvis. Knowing the answer it is easy enough to put two and two together. It is a slight departure from the normal.

DR WYMAN But it could be caused by a mass other than aneurysm?

DR SIMEONE A retroperitoneal abscess might do it as well as any other tumor.

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**COMMUNICATIONS** should be addressed to the *New England Journal of Medicine*, 3 Fenway, Boston 15, Massachusetts.

## NEW DIRECTOR OF CHILDREN'S HOSPITAL

Dr. GUY W. BRUGLER, of Cleveland Heights, Ohio, has been named director of the Children's Hospital of Boston, succeeding Dr. Stanton Garfield, who has been acting director of the institution for the past few months.

Dr. Brugler has been assistant director of University Hospitals in Cleveland since 1939. He was on leave of absence during World War II for two years and was with the United States Army Fourth General Hospital in Australia and New Guinea, with the rank of lieutenant colonel. Subsequently, he was executive officer at the United States Army Woodrow Wilson General Hospital in Staunton, Virginia. His executive and administrative experience will be

invaluable in carrying to completion the plans now underway at the Children's Hospital.

At the large teaching institutions it has long been evident that a mere knowledge of medicine is not enough for the head of what is actually a large corporation, nor is executive ability sufficient. Ideally, there should be a man who not only has a knowledge of medicine and is sympathetic with the needs of the professional staff but also has a sound business sense and administrative experience.

The plans of the trustees of the Children's Hospital are national in scope, and their fulfillment will do much to further the art and science of the medical care of this age group. The harmonious liaison between the professional and the executive sides is of the greatest importance, and it is believed that the trustees of the Children's Hospital, by wisely considering this fact, have made a good choice. We wish them all success and believe that in the appointment of their new director they have taken an important step in furthering their plans and ideals. The successful fruition of their project will result in great benefit, not only to greater Boston and New England but also to the country.

## CHEMOTHERAPY OF TUBERCULOSIS

THE successful use of sulfanilamide and its derivatives and the demonstration of the curative effect of penicillin for many types of infections have led, quite naturally, to renewed efforts to discover a true cure for tuberculosis. Sulfanilamide and those of its derivatives that have proved most successful against the common coccil and bacillary infections have been shown to be bacteriostatic in vitro but have not given encouraging results in the treatment of tuberculous infections. The studies of Rich and Follis<sup>1</sup> on the effects of sulfanilamide in experimental tuberculosis in guinea pigs, although they showed only minimal effects from this agent, have nevertheless laid the groundwork for the testing and screening of various agents for their therapeutic effects in this disease. Modification and standardization of the method by Feldman and his associates have brought out the effectiveness of a succession of chemicals of the sulfone group, including Promin, Diasone and Promizole, each of which gave promise

of only limited usefulness owing to the toxic effects of prolonged treatment with the large doses that are required for any therapeutic benefit<sup>2-5</sup>. The same methods and others involving infections in mice and even in chick embryos have since been used to establish the effectiveness of streptomycin in tuberculosis.

This is not the first or only period, however, when chemotherapeutic success, apparent or real, in the treatment of one type of infection or another has been accompanied by clinical trials and enthusiasm for the same or related agents in tuberculosis. A timely comprehensive and critical review of these and other aspects of the chemotherapy of tuberculosis was ably presented by Hart<sup>6</sup> in his Mitchell Lecture delivered last summer before the Royal College of Physicians in London. This lecture gives a chronologic account of the various agents and classes of agents that have been used during the past century. Although the lecturer's summaries and comments on some of the older types of therapy are of interest from the point of view of historical perspective, his analysis of the present status of the sulfones and of streptomycin and his outlook for the future are particularly significant and worthy of comment.

The experiences to date with the sulfonamides and related compounds are summarized somewhat as follows. They have a more deterrent effect on experimental tuberculosis in some species than any drugs previously tried. Although early established lesions may regress and even be resolved, the eradication of virulent infection, a necessary criterion in the acute or subacute disease of the hypersensitive guinea pig, has not been attained. In man the small number of cases treated, in the absence of simultaneous matched controls in most trials hitherto reported, has made the assessment of these drugs difficult, but the results do not appear so favorable as those in the guinea pig. This is explained either by a lower tolerance, with the result that adequate dosage is difficult to achieve because of the risk of objectionable symptoms or by the possibility that the type of disease is different or that the drug is altered in the body and thus inactivated. At best, some benefit in recent exudative lesions is attributable to these

drugs, but no regression of the disease to quiescence or cure has been demonstrated. The clinical use of these chemotherapeutic agents is likely to be limited to local use or to their employment in combination with other substances, such as streptomycin.

A few years ago, interest in the chemical analysis of the mycobacteria had focused on their fatty structure. Because of this, emphasis was placed on a "lipophilic" approach to the chemotherapy of tuberculosis and search among antiseptics was centered on fat-soluble compounds. Hart properly points out that the results with water-soluble sulfones and with streptomycin emphasize the fact that the mycobacteria, despite their fatty structure, are apparently more susceptible to water-soluble antiseptics than to fat-soluble compounds, thus, the lipophilic approach to chemotherapy does not appear to be the only one, nor may it be the most fruitful.

There are many reasons for investigating the aromatic group of organic compounds for their possible use against tuberculosis. Some have been tested because of their relation to the sulfones, whereas others, such as the naphthaquinone derivatives, represent an attempt to interfere with bacterial metabolism through a structural similarity to hypothetical growth factors or growth stimulants of the vitamin K type. Others were studied in a search for growth inhibitors based on the increase in oxygen uptake by washed suspensions of tubercle bacilli produced by benzoic and salicylic acids and certain other aromatic compounds. Such investigations suggested that these or chemically similar substances may play a part in the normal oxidation of bacilli and that substituted benzoates and salicylates may interfere with the oxidation and so inhibit growth\*. Certain dyes have also been used because of promising earlier results, and some of the acridine compounds have been tested because of their clinical value in protozoal and bacterial infections, whereas others were employed because they were wax-soluble.

None of these substances, however, have as yet given any evidence of efficacy, combined with safety, in human tuberculosis, although some of the clinical

\*Several papers reporting encouraging results from the use of para-aminosalicylic acid both in experimental infections and in clinical tuberculosis have appeared recently in the Swedish literature. Studies of this compound are now also under way in some laboratories and clinics in this country.

trials are not yet complete. One compound, Calciferol, deserves particular mention, however, several French and British workers are noted as having observed good results in lupus vulgaris with this substance used in high dosage. Its exact mechanism of action has not been clarified, and these clinical results require confirmation. Although serious toxic effects have thus far not been reported, the possibility of calcific deposits in tissues must be watched. A long list of antibiotics from natural sources, all of which have antibacterial action against the mycobacteria, is given. The sources of most of these antibiotics are species of *Aspergillus* and *Streptomyces* and organisms related to *Bacillus subtilis*. Among these agents, however, only streptomycin is obtaining a full therapeutic trial. Hart's evaluation of streptomycin is based on the early results. Experimentally, these seem to be much more favorable in guinea pigs than in mice. He believes that the effects in human beings justify cautious enthusiasm. The disadvantages are recognized, particularly the development of resistant strains during treatment, the necessity for prolonged therapy with large doses and the deleterious effect of an acid medium. For these reasons it is thought that other chemotherapeutic agents may prove to be more desirable for use in tuberculosis even should streptomycin justify its present hopes.

The chemical and antibiotic problems involved in the discovery of an effective chemotherapeutic agent, especially in tuberculosis, are ably discussed. Hart states that these two paths should ultimately converge — "for knowledge of the chemical structure of antibiotic substances may promote laboratory synthesis of active related compounds, while knowledge of the point of interference of such substances may give new information on the essential metabolism of the tubercle bacillus and lead to the purposeful creation of simpler synthetic antimetabolites." It is improbable, however, that success in chemotherapy will supersede all the tried and tested methods of control, acquired through the years, that are applied to the patient, to his family and to the community. Rest can be expected to remain the foundation of treatment, surgical methods will be needed in certain types of cases, and the state of housing and of nutrition may be expected to

continue to influence the trend of tuberculosis incidence and mortality. Hart concludes "There are in the world perhaps between ten and twenty million sufferers from active tuberculosis. In order to reduce this inroad on world health we shall probably need most of the reasonable measures — social and economic, preventive and therapeutic — that we possess now or that we can acquire in the future. The attack will remain multiple, the tactics will change."

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#### A HUNDRED YEARS AGO

A revolution is very much needed in the manufacture of boots, the modern fashion of high heels being positively injurious to the frame work of the feet. If the foot is tilted from the top of a high-heeled boot, the toes are pressed forward, down an inclined plane, which distorts them, and leads to the formation of corns. In multitudes of young men, the pressure is so great forward, that the large toe joint and the little toe metatarsal articulations are affected with bunions, swell, and sometimes remain permanently enlarged and sensitive. All beauty and symmetry are forever lost, and to the last days of an extreme old age, a foot thus tortured into a state of disease will be both sore and distorted. Something might also be said of ladies' shoes, with high heels, but as they are victims to other and even worse effects on the chest from a determination to improve upon nature, their case is deferred for another occasion. — The introduction of a foreign body into the larynx, or trachea, is an accident generally attended with much terror and distress at the time, and often followed by symptoms of an alarming, and sometimes of a fatal, character. The occurrence of this accident is rendered more frequent, both by the heedlessness of children, and the foolish habit indulged in by many grown persons, of keeping pins, nails, and other like bodies, in the mouth. Dr. J. Mason Warren reports three interesting cases: the first was a child, who while in the act of laughing, drew a common garden bean, which she had in her mouth, into the

trachea, the second, a little boy, was suddenly seized with a choking and violent cough which he said was caused by a blacksmith's nail in his mouth, the third was a young woman who had been so unfortunate as to get a pin in her larynx, after undressing a child and incautiously putting the pins in her mouth as they were removed from its dress. As Dr. Warren says, a question always arises in the mind of the surgeon called to an instance of this kind as to the propriety of opening the windpipe and attempting the extraction of the foreign body without delay. If the nature of the symptoms be urgent, and immediate suffocation is threatened, there is no alternative but to proceed at once with operation. But if the violent paroxysm, which at first threatened life has subsided, and the substance has settled into one of the bronchial tubes, causing only occasional disturbance, the question becomes one of more difficult solution. Dr. W. avers, should another case of this kind occur to him, he should at once perform the operation of tracheotomy, and by a free use of ether, attempt to allay the irritability of the air passages, so as to allow a more easy exploration by instruments, than is generally afforded in the natural state. — At the annual meeting of the Boylston Medical Society, November 22d, 1847, the following gentlemen were elected officers for the ensuing year: Luther Parker, Jr., M.D., *President*, James W. Stone, M.D., 1st *Vice-President*, Daniel D. Slade, M.D., 2d *Vice-President*, Z. B. Adams, M.D., *Treasurer*, James C. Neilson, *Secretary*, and Edwin Leigh, *Librarian*. Drs. John Ware, Geo. Hayward, Enoch Hale, Z. B. Adams, G. C. Shattuck, Jr., John Homans, Jacob Bigelow, *Trustees*. — A law is needed in Massachusetts requiring every druggist, apothecary and wholesale dealer who desires to keep on hand drugs which may be deadly poisons, to procure a license to do so from the municipal authorities. Perhaps we may be censured for being over careful, and even whimsical in the scheme here proposed for protecting the people, but if so, we have a valid apology. Life is too precious to be subjected to the contingency of death when all danger might be avoided by a simple process. — Dr. C. A. Harris of Baltimore and Drs. Buckminster Brown, and W. T. G. Morton of Boston give us intelligence from Edinburgh of Prof. Simpson's discovery of chloroform as a substitute for ether in preventing the pain of surgical operations. In preparing and administering the substance to a patient, Dr. Morton obtained the polite assistance of Dr. E. R. Smilie, a person of some reputation in chemical science. A lady opportunely arrived at Dr. M.'s office for the purpose of inhaling ether, and having three teeth extracted under its operation. After inhaling ether and allowing its effect to pass away, about one ounce of freshly made chloroform was put upon the sponge previously freed from the effect of the ether, and administered by the usual method. The teeth were

extracted without the knowledge of the patient, Dr. M. says the effects were similar to those produced by ether. The perfume of the new vapor is said to be not unpleasant, but the reversal, and the odor of it does not remain for any length of time obstinately attached to the clothes of the attendant, or exhaling in a disagreeable form from the lungs of the patient. Its exhibition is said to be accompanied by no sickness, vomiting, headache, salivation, or uneasiness of chest. — Extracted from the *Boston Medical and Surgical Journal*, December 1847.

R F

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CANCER AND OTHER CHRONIC DISEASES

In the annual report of the Division of Cancer and Other Chronic Diseases certain figures pertaining to the cancer clinics are interesting. The attendance increased from 1927, the first year of the clinics, until 1940, when it reached a maximum of 5490 new patients, 32 per cent of whom had cancer. During the war years there was a decided drop in attendance, 1943 being the year having the smallest number. The trend has again been reversed, although in 1946 the total attendance of 4026 patients, with 35.4 per cent having cancer, is considerably less than that in 1940.

There has been an increase in the percentage of persons who delayed less than a month between the first appearance of symptoms and first consultation with a physician. In the period 1930-1935, 14 per cent delayed less than one month, and in 1946, 23 per cent. There was considerable difference in the delay depending on the location of the cancer.

In 1946 more patients came to the cancer clinics upon recommendation of physicians than in any previous year, the percentage being 88.8. Of the recommendations made at the clinics 88.5 per cent were carried out within a month.

There has been a great increase in the use of the Tumor Diagnosis Service. In 1926 a total of 2484 specimens were examined, and in 1946, 5264 specimens. In 1926, 371 physicians and 52 hospitals and in 1946, 809 physicians and 108 hospitals made use of this service.

During the war, teaching clinics decreased both in number and in attendance. Although they have not returned to their original extent, 20 clinics, with a total attendance of 781 physicians, were held in 1946.

Several of the tables from the annual report have been multigraphed and are available to the physicians of Massachusetts upon request to the Division of Cancer and Other Chronic Diseases, Massachusetts Department of Public Health, 100 Nashua Street, Boston 14.

## THE CYTOLOGY TEST FOR CANCER

The Massachusetts Department of Public Health, in co-operation with the cancer clinics, has been carrying on an investigation of the cytology test for cancer of the uterus. This study, financed in part by the Commonwealth Fund, was inaugurated to determine the incidence of cancer of the uterus in women without gynecologic symptoms, whether this test is of sufficient value to warrant its continued use in the cancer clinics and whether it should be offered to all physicians in Massachusetts as another diagnostic service. An advisory committee for this study was appointed, consisting of Drs Thomas Almy, John Fallon, Reginald Fitz, Maurice J. Remont-Smith, Edward G. Huber, Joe V. Meigs and Shields Warren. Since the formation of this committee Dr Almy and Dr Huber have died.

The committee recommended collecting vaginal smears from women attending the cancer clinics, from both those with and those without gynecologic symptoms. Biopsies were obtained from as many patients with positive smears as possible. In some cases the smear diagnosis was confirmed, in others, it was not. It is desired that three years after the original smear these women have a repeat smear as well as a pelvic examination, to determine whether or not cancer is present. The follow-up smear should disclose whether the unconfirmed positive smears were falsely positive, as well as whether the negative smears were falsely negative.

The first half of the study has been completed, and preliminary indications are that the true rate of uterine cancer among symptom-free women lies between 2 and 4 per 1000, whereas that among women with gynecologic symptoms may lie between 75 and 100 per 1000.

Until the study is completed this diagnostic procedure will not be offered to physicians in the State, but so far as facilities permit, the examination of smears collected at the clinics will continue.

## MISCELLANY

## NOTES

Dr. Walter S. Burrage of Boston, has been elected to the board of trustees of the American Allergy Fund, a national foundation for the support of scientific research and public education in the field of allergy. Dr. Burrage is assistant professor of medicine at Harvard Medical School and chief of allergy for the Veterans Administration, Branch No. 1. He is consultant at the United States Naval Hospital in Chelsea, physician at New England Deaconess Hospital and consultant at Massachusetts Eye and Ear Infirmary in Boston.

The American Allergy Fund has its headquarters in Cleveland, Ohio, and its president is Dr. Jonathan Forman, editor of the *Ohio State Medical Journal*. Dr. Sanford B. Hooker of Boston University School of Medicine, is an associate of the fund and a member of its scientific advisory council, which is headed by Dr. A. J. Carlson of the University of Chicago.

Dr. Samuel C. Harvey, formerly William H. Carmalt, Professor of Surgery and chairman of the Department of Surgery, Yale University School of Medicine, was recently appointed professor of surgery with special reference to oncology (the study of tumors) at the School of Medicine. The new professorship is supported by grants from the National Cancer Institute of the United States Public Health Service and Mr. Robert E. Hunter of Pasadena, California. Dr. Harvey will assume responsibility for stimulating investigation of the problem of cancer and for training medical students and physicians in the special problems involved in the diagnosis, treatment and care of patients with this disease. His successor in the Department of Surgery is Dr. Gustaf T. Lindskog, formerly associate professor of surgery.

## NORWOOD HOSPITAL

At a meeting of the senior staff of the Norwood Hospital on November 7, the following resolution was passed:

The Norwood Hospital Staff notes with regret the death of our late colleague Dr. Louis Arkin.

Dr. Arkin was a member of the Associate Staff of the Norwood Hospital from March 1945, to his death on October 1, 1947. In that time, he gained the respect and affection of the members by his ethical conduct and good fellowship. The Norwood Hospital Staff express deep regret at his passing and extend sincere sympathy to his bereaved relatives.

It is hereby resolved that a copy of this action be included in the records of the Norwood Hospital Staff and similar copies be sent to his nearest relative and published in the *New England Journal of Medicine*.

## CORRESPONDENCE

## RESTORATION OF LICENSE

To the Editor: At a meeting of the Board of Registration in Medicine held October 17, it was voted to restore the registration to practice medicine in this Commonwealth to Dr. Morris J. Kupper, 961 Blue Hill Avenue, Roxbury, whose registration was revoked October 18, 1944.

H. QUIMBY GALLUPE, M.D. Secretary

State House  
Boston

## LEAD PAINT STILL A HAZARD

To the Editor: In the November 6 issue of the *Journal* there appears an editorial entitled "Epidemic Lead Poisoning." This title is supported by the facts presented and unquestionably explains how large numbers of infants and children may become victims of this disturbance at any one time, or as one might say at any one exposure. The main point of the editorial is well taken and most assuredly merits the attention of the medical profession. However, it is unfortunate that the editorial places lead poisoning resulting from the ingestion of lead paint obtained from toys, cribs and so forth and chewed by infants and young children in the background. Actually, this source of lead poisoning continues to be a real and not a mythical danger. A review of the cases of acute or chronic plumbism occurring among this age group will verify this statement. The manufacturers may not employ lead paint in painting their wares, but what type of paint does the average adult select in repainting cribs, toys and interior woodwork? There is adequate clinical evidence that he employs lead paint, and thus the young patients suffering from plumbism continue to present themselves at hospitals. They do not appear in epidemic proportions, but the total number over a given period proves startlingly high.

It therefore does not appear as suggested in the editorial that emphasis has sometimes been mistakenly placed by the medical profession on the source of lead in lead poisoning occurring among infants and children. One case of acute poliomyelitis does not make an epidemic, but its occurrence is disturbing to the parents and, as with lead poisoning, may prove disastrous if not fatal to the victim. It is the little things that count—even if it is only an old toy repainted with lead paint by a devoted parent.

R. CANNON ELEY, M.D.

300 Longwood Avenue  
Boston.



## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Arthritis and Related Conditions* Edited by Theodore F. Bach, M.D., associate in medicine, Graduate School of Medicine, University of Pennsylvania, and chief, Arthritic Clinic, Abington Memorial Hospital, Abington, Pennsylvania. 8°, cloth, 472 pp., with 139 illustrations. Philadelphia: F. A. Davis Company, 1947. \$6.50

*Deep Analysis: The clinical study of an individual case* By Charles Berg, M.D. (Lond.), D.P.M., fellow of the British Psychological Association, physician, British Hospital for Functional Mental and Nervous Disorders, and physician, Institute for Scientific Treatment of Delinquency. 8°, cloth, 254 pp. New York: W. W. Norton and Company, Incorporated, 1947. \$3.50

*Osteotomy of the Long Bones* By Henry Milch, M.D., consulting orthopedist, Maimonides Hospital, and attending orthopedic surgeon, Hospital for Joint Diseases and Riverside Hospital, New York City. 8°, cloth, 294 pp., with 181 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$6.75

*Textbook of the Nervous System: A foundation for clinical neurology* By H. Chandler Elliott, M.A., Ph.D., assistant professor of anatomy, Medical College of the State of South Carolina. With an introduction by Wilder Penfield, M.D. 4°, cloth, 384 pp., with 158 illustrations. Philadelphia: J. B. Lippincott Company, 1947. \$8.00

*Cineplasty* By Henry H. Kessler, M.D., Ph.D., orthopedic and amputation consultant, Office of Vocational Rehabilitation, and member of New Jersey Rehabilitation Commission. With a foreword by Ross T. McIntire, Vice-Admiral (MC), U.S.N., the Surgeon General, United States Navy. 8°, cloth, 201 pp., with 199 illustrations. Springfield, Illinois: Charles C. Thomas, 1947. \$6.75

## NOTICES

## NEW ENGLAND SOCIETY OF PHYSICAL MEDICINE

A meeting of the New England Society of Physical Medicine will be held at the Hotel Kenmore, Boston, on Wednesday, December 17, at 8 p.m. Dr. Sidney Licht, editor of *Occupational Therapy and Rehabilitation*, will speak on the subject "Clinical Diagnostic Measures in Physical Medicine."

Physicians, physical therapists and nurses are invited to attend.

## AMERICAN COLLEGE OF SURGEONS

Six sectional meetings of the American College of Surgeons will be held in 1948. The date and location of each meeting is as follows: January 20 and 21, Commodore Perry Hotel, Toledo, Ohio; January 26 and 27, Ansley Hotel, Atlanta, Georgia; January 30 and 31, Oklahoma Biltmore Hotel, Oklahoma City; March 1 and 2, Cosmopolitan Hotel, Denver, Colorado; March 15 and 16, Hotel Nicolle, Minneapolis, Minnesota; May 17 and 18, The Nova Scotian, Halifax, Nova Scotia. Fellows of the College, the medical profession at large and hospital personnel are invited. Each meeting will be two days in length and will include conferences for hospital personnel and sessions for the medical profession. The showing of medical motion picture films will begin each day's program at 8:30 a.m. There will be luncheon meetings each day and a dinner meeting on the first evening followed by a symposium on cancer. Panel discussions on scientific subjects, led by internationally known authorities in each field of surgery, will be held each morning and afternoon.

## SOCIETY MEETINGS AND CONFERENCES

## CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 18

## FRIDAY, DECEMBER 19

\*9-10-10:00 a.m. Gastritis. Dr. Seymour Gray. Joseph H. Pratt Diagnostic Hospital.

\*10:00 a.m.-12:00 p.m. Medical Staff Rounds. Peter Bent Brigham Hospital.

## MONDAY, DECEMBER 22

12:00 p.m. Clinicopathological Conference. Margaret Jewett Hall, Mount Auburn Hospital, Cambridge.

\*12:15-1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

## TUESDAY, DECEMBER 23

\*12:15-1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

## WEDNESDAY, DECEMBER 24

\*12:00 p.m. Grand Rounds and Clinicopathological Conference (Children's Hospital). Amphitheater, Peter Bent Brigham Hospital.

\*2:00-3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.

\*Open to the medical profession.

DECEMBER 15-17. American Academy of Allergy. Page 602, issue of October 16.

DECEMBER 16. Greater Boston Medical Society. Page 886, issue of December 4.

DECEMBER 16. Experiences in the Pacific Area. Dr. Merrill Moore. South End Medical Club. 12:00 p.m. 554 Columbus Avenue, Boston.

DECEMBER 17. New England Society of Physical Medicine. Notice above.

JANUARY-APRIL. Thirteenth Postgraduate Seminar in Neurology and Psychiatry. Metropolitan State Hospital. Page 348, issue of August 22.

JANUARY 8. Dysmenorrhea. Dr. Joe V. Meigs. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

JANUARY 20 AND 21. American College of Surgeons. Commodore Perry Hotel, Toledo, Ohio. Notice above.

JANUARY 26 AND 27. American College of Surgeons. Ansley Hotel, Atlanta, Georgia. Notice above.

JANUARY 30 AND 31. American College of Surgeons. Oklahoma Biltmore Hotel, Oklahoma City. Notice above.

FEBRUARY 6. American Board of Obstetrics and Gynecology. Page 242, issue of August 14.

MARCH 28-APRIL 4. American Association of Industrial Physicians and Surgeons, American Industrial Hygiene Association, American Conference of Governmental Industrial Hygienists, American Association of Industrial Nurses, Inc., and American Association of Industrial Dentists. Hotel Statler, Boston.

APRIL 19-23. American College of Physicians. Page xiii, issue of July 31.

MAY 6-8. American Association for the Study of Goiter. Page xiii, issue of July 31.

MAY 17-20. American Urological Association. Hotel Statler, Boston.

MAY 18-22. American Association on Mental Deficiency. Copley Plaza, Boston.

MAY 25-27. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.

## DISTRICT MEDICAL SOCIETIES

## FRANKLIN

JANUARY 13

MARCH 9

MAY 11. Annual Meeting. Hotel Weldon.

All other meetings will be held at Franklin County Hospital.

## MIDDLESEX EAST

JANUARY 21

MARCH 24

MAY 12. Annual Meeting.

All meetings will be held at the Bear Hill Golf Club.

## NORFOLK

JANUARY 27. Round-Table Discussion. Bleeding from the alimentary tract.

FEBRUARY 24. Obstetric and Gynecologic Night.

MARCH 23. Harvard Night.

## PLYMOUTH

JANUARY 15. Brockton Hospital, Brockton.

FEBRUARY 19. Toll House. Whitman.

MARCH 18. Goddard Hospital, Brockton.

APRIL 15. State Farm. Bridgewater.

MAY 20. Lakeville Sanatorium, Lakeville.

## WORCESTER

JANUARY 14. St. Vincent's Hospital.

FEBRUARY 11. Worcester State Hospital.

MARCH 10. Memorial Hospital.

APRIL 14. Hahnemann Hospital.

MAY 12. Annual Meeting.

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## ANESTHESIA WITH INTRAVENOUS PENTOTHAL SODIUM AND LOCAL NERVE BLOCK IN GYNECOLOGIC SURGERY\*

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THE use of Pentothal Sodium as an intravenous anesthetic agent has found wide acceptance in the field of gynecologic surgery. This is probably related to the following basic considerations: the high incidence of satisfactory muscular relaxation in this field of surgery as a consequence of antecedent pregnancy, and the minimal intensity of reflex stimulation of respiration from surgical trauma in the areas of lumbar and sacral autonomic nerve supply during pelvic surgery. Quantitative and pneumographic observations made during the past three years in pursuance of a routine surgical practice in which intravenous Pentothal Sodium combined with local nerve block has provided the anesthetic of choice in 60 to 70 per cent of 2000 cases of general surgical procedures have elucidated the variations in reflex stimulation of respiration not only in the peripheral area of distribution of the nerves from the lumbar and sacral segments of the cord but also in the areas of distribution of the peripheral nerves derived from the other neurologic segments.

A sufficient volume of gynecologic surgery is included in this over-all experience to warrant a detailed evaluation of this combined method of anesthesia. In the total of 2000 general surgical cases operations were performed under Pentothal Sodium in 450 cases that were in the field of gynecologic surgery. Of this selected group, there were 236 intra-abdominal major gynecologic procedures, 40 major vaginal procedures (vaginal hysterectomy, Fothergill operation and interposition) and 170 minor vaginal procedures. Any analysis of such an experience should be made in the light of the major physiologic facts revealed in this study as they relate to the neurospecific segmental character of the traumatic reflex stimulation of respiration in the several neurologic segments of the body. Specifically, three neurologic segments are trauma-

tized surgically during surgery in the pelvis. The incision and closure of the abdomen, as well as the retraction of the abdominal viscera upward for exposure of the pelvis, are carried out in the strongly reactive areas of distribution of the thoracic nerves; the removal of the uterus itself is carried out in two different neurologic regions of minimal reactivity—the areas of the lumbar and sacral autonomic nerves.

In general it may be stated with reference to the over-all quantitative requirements of Pentothal Sodium in any particular surgical procedure, that the rate of administration will be related to two determining factors: the need for the drug in any particular case as determined by the rate of metabolic destruction of the drug, and the duration of the operation and its type according to the neurologic segment in the peripheral area of distribution of the nerves of which the operation occurs. Detailed quantitative studies have revealed no other important determinant of the rate of utilization of the drug, such as age, sex or weight. Patients of the same sex, age and weight who undergo identical operative procedures show extreme variations in the quantity of Pentothal required for anesthesia. This can be related only to the varying individual rates of destruction of the drug and to the varying intensities of traumatic reflex stimulation of respiration. The prolonged operations entail progressive severance of pathways of nerve conduction that also progressively reduces the number and intensity of stimulating pain impulses transmitted centrally to the respiratory center. As a corollary, this effect steadily reduces the reflex stimulation of respiration and thus diminishes the quantity of Pentothal required to control respiration. With adequate evaluation of these factors there is no residual concrete evidence to indicate the occurrence of any so-called "cumulative action" of the drug. On the contrary, with reflex factors well controlled by procaine field block, there seems to be ample evidence of fixed, level, basic need for the drug in each patient, even over an extended period.

\*Presented at a meeting of the New England Obstetrical and Gynecological Society, Worcester, Massachusetts, May 29, 1946.  
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All intra-abdominal pelvic operative procedures in this group of gynecologic cases were carried out under anesthesia by combined intravenous drip of Pentothal Sodium in a 1 per cent solution and local nerve block by procaine in a 1 per cent solution. The Pentothal was administered by infusion during the induction period at a rate of 250 drops a minute until the patient lost consciousness and stopped counting. No further administration of the drug was made until the early irregularities of respiration returned to normal. Subsequent induction fractions were given in quantities of 10 cc for patients under fifty years of age, with a minute intervening between fractions, or in quantities of 5 cc in thin, small patients over fifty years of age, with two minutes intervening. These induction fractions were repeated for an average of two to four fractions, or for as many fractions as were needed to reach the point of complete induction of surgical anesthesia. Induction was never carried beyond the point of loss of motor response to a pinch of the inner arm or axilla with an Allis forceps, except as further administration of the drug was balanced against the stimulus of respiration by the surgeon who was making the incision. The final end point of complete induction was taken as that at which, in the unconscious patient, there was neither motor response nor undue reflex stimulation of respiration in response to sectioning the body wall.

Subsequent maintenance fractions of Pentothal are administered during the course of the surgical procedure at the rate of 130 drops a minute, each fraction being given when recurring reflex stimulation of respiration by surgical trauma manifests itself. Care is taken never to permit an anesthetized patient to re-enter a too light plane of anesthesia in which the intensity of the reflex stimulation of respiration, particularly in the thoracic-nerve segment (the base of the neck to the symphysis pubis), would handicap the surgeon by disturbing the quiet of the operative field. These subsequent maintenance fractions are limited to quantities of 5 cc with at least one minute intervening between fractions, if the complete induction dose has been less than 75 cc (0.75 gm). In contrast, when the induction dose is over 75 cc, subsequent maintenance fractions of 10 cc each are administered with at least a minute intervening. These fractions are given only to the point of re-establishing control of the reflexly stimulated respiration, the one exception being that, when a local procaine field block (anterior splanchnic, intercostal or pelvic nerve) supplements the Pentothal anesthesia, it should be determined empirically whether the fractions should again be reduced to 5 cc quantities because of the diminished reflex stimulation of respiration. In the abdominal approach to pelvic surgery there were a handful of operations done in the presence of extreme obesity in which Pentothal had to be dis-

continued and ether substituted because of the overly active stimulation of respiration by upward retraction of the abdominal viscera against the diaphragm. A few cases were rejected for Pentothal anesthesia primarily because of an anticipated unsatisfactory respiratory experience from this compression reflex that is discussed below. In vaginal operative work a method of continuous administration of Pentothal and ether is used in which after the usual induction dose of Pentothal in 1 per cent solution, the drug is administered continuously in a 0.5 per cent solution at the rate of 30 drops a minute. Frequently, a 0.25 per cent solution is used at the rate of 30 drops a minute to avoid respiratory depression. Ether is administered continuously at the rate of approximately 28.3 gm an hour. These minimal quantities of drug in combination provide an extremely quiet, satisfactory anesthesia for vaginal operative work. In combined vaginal and abdominal pelvic surgery after a 2-gm ceiling of Pentothal has been reached, ether alone is used to complete the operation.

Transincisional procaine block of the intercostal nerves to the lower half of the rectus muscles is carried out after complete incision of the skin, subcutaneous tissues and fascial anterior layer of the rectus sheath. Injection of these nerves is made at the outer border of the rectus sheath at points 1.5 cm apart, 2 or 3 cc of procaine solution (1 per cent) being injected at each point. An additional 5 cc is injected deeply into each rectus muscle at the upper angle of the incision aiming at the outer sulcus, where the intercostal nerves enter the sheath. This transincisional procedure requires from 30 to 40 cc of procaine solution, and is easily accomplished in two or three minutes. It provides a flaccid paralysis of the rectus muscles such as obtains in spinal anesthesia or deep third-stage ether anesthesia. Only respiratory inactivation of the other abdominal muscles, which is easily accomplished by Pentothal, and not paralysis is needed to provide a satisfactory operative field. In cases in which a pelvic field block is done, 4 cc of procaine is injected retroperitoneally in the region of the superior hypogastric plexus (lumbar-autonomic) immediately below the promontory of the sacrum. An additional 4 cc is injected deeply in the region of the inferior hypogastric plexus (sacral-autonomic), each round ligament is injected at its outer end with 1 cc of procaine solution, at each side of the cervix 3 cc of procaine is injected into the paracervical and parametrial tissues in which the large ganglions of Frankenhäuser lie. Although it does not greatly reduce the quantity of Pentothal used, such a block assures immobility in the abdominal field by completely eliminating reflex activation of the abdominal muscles during expiration as a part of the traction reflex discussed below.

Relaxation of the rectus muscles is routinely produced by procaine nerve block in this method.

Relaxation is never required of Pentothal alone, since muscular relaxation is frequently not achieved under Pentothal alone at a plane of anesthesia that is quite satisfactory in every other respect, conversely, to require muscular relaxation in such cases sometimes entails precipitating a degree of respiratory depression that is wholly unnecessary from all other aspects of a satisfactory degree of anesthesia. The routine use of rectus sheath block is justified by a study of the incidence of full, flaccid muscular relaxation in a series of 100 consecutive cases that had been carried to a satisfactory plane of surgical anesthesia in all other respects (unconsciousness, and the absence of motor response or of undue reflex stimulation of respiration by surgical trauma). An analysis of these cases shows that a striking relation exists between a satisfactory degree of relaxation of the rectus muscles under Pentothal anesthesia alone and the experience of a previous pregnancy with its associated stretching of the abdominal muscles. Of 36 female patients exhibiting a satisfactory degree of relaxation of the rectus muscle at an otherwise adequate plane of anesthesia, 26, or 72 per cent, had experienced a preceding pregnancy. Of 35 female patients who failed to exhibit a satisfactory degree of relaxation at an otherwise satisfactory plane of anesthesia, there were 25, or 71 per cent, who had not experienced previous pregnancy. In a group of 29 male patients, all spared by nature from this physiologic stretching of the abdominal muscles, there were only 3, or 13 per cent, who exhibited satisfactory muscular relaxation, whereas 26, or 87 per cent, failed to exhibit such relaxation. A second grouping of the figures, which encompassed 41 female patients who were subjected to identical surgical procedures through similar incisions (appendectomy through a low right paramedian incision), all reflex factors involved being thus stabilized, showed that of 13 patients who exhibited satisfactory muscular relaxation at the usual plane of anesthesia, 11 had experienced previous pregnancy, on the other hand, of the 28 patients who failed to exhibit satisfactory muscular relaxation, 23 had not previously been pregnant. Procaine injection of the rectus muscles avoided need of a deep plane of Pentothal anesthesia, with its concomitant depression of respiration, and achieved an eminently safe type of anesthesia.

The more powerful intra-abdominal reflexes that condition muscle tensing can also be controlled by the supplemental use of cyclopropane, ether or curare with Pentothal instead of procaine, as shown by the pneumograph, but not so effectively with nitrous oxide and oxygen. In a group of 450 gynecologic operations carried out under combined Pentothal and local nerve block there were only 2 deaths, both of which occurred during convalescence. One was due to an unannounced massive pulmonary embolus, and the other to fatal uremia secondary to

diabetic acidosis. This gives an over-all mortality of 0.4 of 1 per cent for the entire group and 0.7 of 1 per cent for the major surgical procedures. No pulmonary complications other than infarcts of embolic origin were encountered.

A quantitative study of the effect of procaine field block in pelvic surgery on the rate of utilization of Pentothal was made. This study parallels two previous reports, one in cholecystectomy (anterior splanchnic block) and the other in radical mastectomy (intercostal nerve block). Two series of hysterectomies were investigated for comparison. In the first, 10 hysterectomies were done under Pentothal and rectus sheath block alone without procaine field block of the pelvis, in the second, 10 hysterectomies were done with supplemental procaine field block of the pelvis, as described above. The two series are compared with each other only on the basis of the time consumed and the quantity of Pentothal administered during the performance of the hysterectomy per se. This excludes the time interval and the drug administration pertaining to the opening and closure of the abdomen, and the packing up of the viscera. This restriction is necessary to eliminate the highly reactive and variable stimulation of respiration by trauma in the thoracic zone in which the opening, closure and retraction occur, and to limit the study to the effect of reflex stimulation of respiration from trauma in the lumbosacral autonomic zone, which is the neurologic zone involved in a hysterectomy. In the hysterectomies done under Pentothal anesthesia without field block of the pelvis, the average rate of utilization of Pentothal during the hysterectomy per se was 0.006 gm a minute. In the hysterectomies done under Pentothal anesthesia supplemented by procaine field block of the pelvis the rate of utilization of Pentothal was 0.003 gm a minute. This represents a reduction of 50 per cent in the need for Pentothal as a result of the peripheral blockage of all pain impulses initiated by trauma in the pelvis from impinging on the respiratory center. This result parallels the reported reduction of 50 per cent in the need of Pentothal effected by local procaine field block in cholecystectomy (anterior splanchnic block) and in radical mastectomy (intercostal block). The low rate of utilization in the mildly reactive lumbosacral segment (0.006 gm a minute) for hysterectomy stands in the striking ratio of 1:4 when compared with the calculated rate of utilization (0.024 gm a minute) in the highly reactive field of the thoracic segment for cholecystectomy. The minimal intensity of the stimulating impulses arising in the lumbosacral autonomic area is further emphasized by the fact that only 14 per cent of the total amount of Pentothal sodium administered for the entire surgical episode was given during the period of hysterectomy proper, whereas the remaining 76 per cent was required for induction, opening and closing of the

incision (thoracic segment) These indirect quantitative measurements of the segmental differences of intensity of the stimulating impulses that reflexly activate respiration only serve to verify the appended observations on the intensity of segmental reflexes recorded by the pneumograph

Pneumographic studies carried out in the operating room during the course of these studies have demonstrated the specific character of the respiratory response to pain impulses initiated by trauma in the area of distribution of the nerves from the several neurologic segments of the body (cranial, cervical, thoracic, lumbar and sacral) In the cervical segment there is negligible reflex stimulation

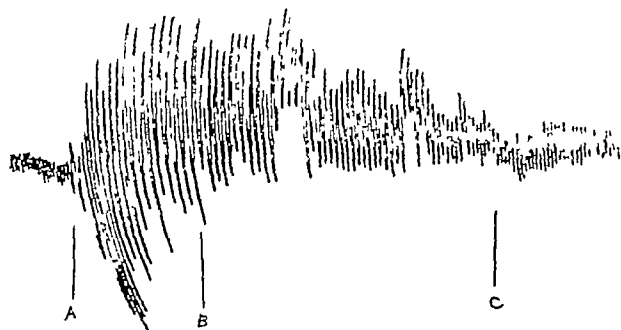


FIGURE 1 Thoracic Somatic Reflex

This graph demonstrates the normal respiratory curve under Pentothal to point A, at which the incision is started. A to B shows the sharp reflex stimulation of respiration with an accentuated and prolonged expiratory phase (upstroke of pen) by pain impulses from incision. The abdominal muscles vigorously contract during expiration, causing muscular rigidity and disturbed abdominal relaxation. Control of reflex stimulation (B to C) with Pentothal is effected by suppressing the expiratory neurons and inactivating (not paralyzing) the abdominal muscles. This restores abdominal relaxation. From C easy, adequate respiration with a quiet abdomen prevails.

of the inspiratory side of respiration in the somatic plane, there is practically no stimulation of respiration in the visceral plane (thyroidectomy). In the thoracic zone (the base of the neck to the symphysis pubis) there is an intense reflex stimulation of the expiratory side of respiration by trauma, both in the somatic and in the visceral plane. This response far exceeds that noted in any other segment of the body. Its importance lies in the fact that stimulated respiration in this segment activates the abdominal muscles in the role of accessory expiratory muscles of respiration, their activity being identical with that which occurs during the forced expiration of heavy exertion or dyspnea. This activity disturbs abdominal relaxation and limits access to the operative fields. In the thoracic visceral zone the reflex muscular response may be of such magnitude in light planes of Pentothal anesthesia as to precipitate an expiratory arrest of respiration during the period of traumatic stimulation, leading to increased production of carbon dioxide from muscular contraction and to deficient oxygen intake, both of

which may contribute to transient cyanosis. Such anoxia is due not to the action of the drug *per se* but to prolonged expiratory muscular response to trauma in a too light plane of Pentothal anesthesia.

A pneumographic recording made while the skin of the lower abdomen (thoracic segment) was being incised showed that, after a period of a quiet, unstimulated run, the trauma of an incision evokes a sharp respiratory response chiefly on the side of expiration (Fig 1). This stimulation of respiration, which activates the abdominal muscles to prolonged and forceful contractile efforts, requires significant amounts of Pentothal to control the stimulated respiratory center and to restore the abdominal muscles to an inactive state at which abdominal relaxation again prevails. Of importance during pelvic surgery is the fact that a similar activation of respiration in the visceral thoracic region may be elicited by compressing the viscera upward against the diaphragm. This compression reflex (Fig 2) manifests itself on the pneumograph by an abrupt shift of the thorax to the position of extreme inspiration as indicated by an abrupt downward shift in the level of the curve. Superimposed on this



FIGURE 2 Thoracic Compression (Visceral) Reflex

The first segment of the chart shows normal respiration with the abdomen opened. The next depressed level of the curve is due to compression of the viscera and fatty mesenteries upward against the diaphragm in obese patients. This opens the thorax to the position of extreme inspiration (downstroke of pen). Sharp, irregular, forced expirations press the viscera downward toward the pelvis. The final high portion of the curve (needle elevated) shows the undesirable degree of depression of respiration with Pentothal necessary to control this forceful reflex in extremely obese patients, abdominal relaxation being restored.

lowered curve are jerky, irregular respiratory efforts. These efforts, which are due to reflex activation of the abdominal muscles as accessory expiratory muscles of respiration, cause expiratory protrusion of the retracted viscera into the pelvis. The compression reflex is activated in the presence of extreme obesity by pressure of the viscera against the diaphragm. It may be one of the most powerful and persistent reflexes in the body, requiring such undesirably large quantities of Pentothal to suppress it as to make the supplemental use of some other agent, such as cyclopropane, or ether, desirable. This compression reflex is not activated in the average pelvic case in nonobese patients.

The reflex activation of respiration in the lumbar visceral zone (autonomic) consists of a minimal increase in the amplitude and rate of respiration. There is no activation of the abdominal accessory muscles of expiration, so that abdominal relaxation is not disturbed. The character of the response is shown in Figure 3, which demonstrates that, after a brief quiet run without trauma, crushing and pulling of the presacral lumbar nerves (superior hypogastric plexus) causes a definite but slight increase in the amplitude and rate of respiration. Procaine injection above the level of trauma in the region of the lumbar plexus obliterates first the stimulus to the rate of respiration and secondly the stimulus to the amplitude of respiration. This minimal respiratory response to trauma in the



FIGURE 3 Lumbar Visceral Reflex

The chart illustrates a normal unstimulated run up to point A. Between A and B an increase in rate and amplitude from traction and squeezing of the presacral nerve plexus (superior hypogastric) occurs. At point B procaine injection above the point of trauma causes an immediate reduction in the rate and a gradual reduction in the amplitude of respiration. At point C after the proximal end of the plexus has been severed a fixed slower rate and a reduced amplitude are established.

lumbar autonomic zone increases the need for additional Pentothal administration very little if any.

Trauma in the area of distribution of the sacral autonomic nerves elicits two characteristic types of respiratory response, both of which are induced by traction on the uterus, which in turn establishes tension in the uterosacral ligaments. The first type of reflex response to traction is inspiratory, and the second is expiratory. The two types of response do not occur simultaneously in the same patient. There is but a momentary response to each movement of traction, in contrast to the prolonged, repetitive types of response to trauma in the other neurologic zones. Figure 4 demonstrates the first type of inspiratory response to traction. Each movement of traction on the uterus — even after all attachments above the cervix have been severed and the vaginal cuff has been completely detached from the cervix anteriorly and laterally so that only the posterior uterosacral region remains intact — is followed by a single prolonged inspiratory effort

accompanied by a single transient, moaning phonation due to a moderate transient laryngospasm. Deep injection of procaine solution in the immediate vicinity of the inferior hypogastric plexus (sacral autonomic) completely obliterates this response to

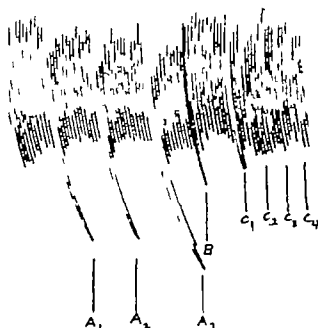


FIGURE 4 Sacral Visceral (Inspiratory) Reflex

Individual tractions on the uterosacral ligaments at points A<sub>1</sub>, A<sub>2</sub> and A<sub>3</sub> evoke single prolonged inspiratory responses, associated with reflex moaning laryngeal phonation. At point B (kymograph stopped) a deep presacral injection of procaine (inferior hypogastric plexus) has been made. Subsequently a single minimal response occurs with traction at point C<sub>1</sub> from incomplete procainization whereas traction at points C<sub>2</sub>, C<sub>3</sub> and C<sub>4</sub> shows complete elimination of all inspiratory responses and laryngeal phonation after complete procainization. This reflex is mediated via the sacral autonomic nerves in the uterosacral ligaments. Abdominal relaxation is not disturbed by this reflex since the abdominal muscles are not activated during expiration.

traction. In some cases it was noted that this unique response was elicited only when the tractile effort coincided with the peak of expiration, it did not occur when the traction coincided with the peak of inspiration. In the second type of expiratory response to traction there are brief episodes of expiratory response occurring coincidentally with traction on the uterus (Fig. 5). The response does not outlast the tractile effort and persists for only one to three respiratory cycles. The response could be elicited whether the tractile effort coincided with the peak of inspiration or the peak of expiration. This expiratory response is also obliterated by deep sacral procaine block of the inferior hypogastric plexus, indicating as in the first type of response that it is a reflex mediated through the sacral autonomic plexus of nerves. Furthermore, both types of reflex response were obliterated by procaine infiltration of the uterosacral ligaments, demonstrating that the afferent nerve fibers that conduct activating pain impulses into the sacral plexus traverse these autonomic structures. These sacral reflexes may be a factor in pelvic and low-back pain when the uterosacral ligaments are involved by conditions such as

pelvic inflammatory disease and endometriosis. In the first type of inspiratory response to traction there is no activation of the abdominal expiratory muscles and hence no disturbance of abdominal relaxation. There is consequently no need for increased quantities of Pentothal. In the second type of expiratory response there is a brief tensing of the

tively by the pneumograph and bears out the quantitative observations.

### SUMMARY

A report on the use of combined intravenous Pentothal sodium and local nerve block as a method of anesthesia in gynecologic surgery is presented. The safety of the method is attested by the fact that the over-all mortality for the entire group was 0.4 of 1 per cent and that for the major gynecologic procedures was 0.7 of 1 per cent, with no relation between mortality and anesthesia.

Two parallel groups of hysterectomies were done, the first without and the second with procaine field block of the pelvis. There was a 50 per cent reduction in the rate of utilization of Pentothal from 0.006 gm. a minute without field block to 0.003 a minute with the field block. This parallels the 50 per cent reduction in the rate of utilization of Pentothal as reported previously in cholecystectomy by anterior splanchnic block and in radical mastectomy by intercostal nerve block.

The major importance of a previously experienced pregnancy in determining a satisfactory degree of muscular relaxation under Pentothal anesthesia alone is indicated. The supplemental method of rectus muscle block with procaine provides a flaccid paralysis of the muscles routinely, so that surgery may be done in relatively light planes of Pentothal anesthesia that are wholly free from respiratory depression.

Pneumographic tracings demonstrating the characteristic patterns of reflex response of respiration to trauma in the three neurologic fields involved by surgical trauma during pelvic surgery (thoracic, lumbar and sacral) are presented.

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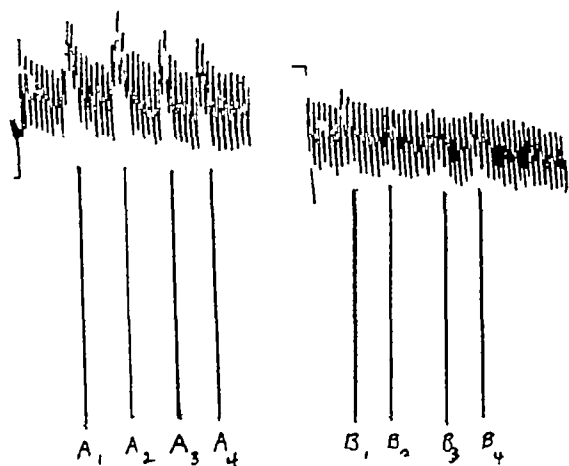


FIGURE 5 Sacral Iisceral (Expiratory) Reflex.

At the successive points of elevation of the curves A<sub>1</sub>, A<sub>2</sub>, A<sub>3</sub> and A<sub>4</sub>, which coincided with traction on the uterus, there was moderate tensing of the abdominal muscles during expiration for one to three respiratory cycles. Even though the traction continued, the stimulus disappeared, and the curve returned to its initial level. This slight tensing of the abdominal muscles caused a transient downward crowding of the retracted viscera toward the pelvis. As demonstrated in the second portion of the curve, this reflex is also obliterated by procainization of either the utero-sacral ligaments or the sacral plexus (inferior hypogastric). Traction at B<sub>1</sub>, B<sub>2</sub>, B<sub>3</sub> and B<sub>4</sub> shows no significant expiratory response. There is never any laryngeal phonation with this expiratory reflex, which is mostly tonic in character.

accessory expiratory muscles of the abdomen with each traction, which in turn causes a slight momentary protrusion of the retracted viscera downward toward the pelvis. This reflex leads to a moderate increase in the rate of administration of Pentothal for its control. However, in both types of response the minimal character of the activation of respiration by surgical trauma in the sacral autonomic as well as in the lumbar region is demonstrated qualita-

## BRONCHIECTASIS TREATMENT AND PREVENTION\*

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**BRONCHIECTASIS** is protean in its expressions as it is sometimes obscure in its origin. The clinical picture varies in individual patients, but common to the severer cases is a history of harassing, recurrent pulmonary infection, head colds or sinusitis that "goes down into the chest," to remain for weeks with a productive cough, or one of recurrent hemoptyses or repeated attacks of pneumonia. As a rule, severe pulmonary infections date the onset of the symptoms of bronchiectasis. With great clarity patients recall childhood and adult pneumonias, measles and whooping cough, influenza and "croup" as the beginning of the pulmonary trouble. In many cases each succeeding reinfection aggravates the symptoms. Patients with extensive disease may be seriously toxic with fever, abundant sputum, often foul smelling, a poor appetite, inability to gain weight and physical weakness. Psychologically, some of them are problems of adaptation to a life of severe invalidism in a society in which their presence may be offensive because of cough and the bad odor of their secretions. If surgery is unsuitable for them, they become a difficult problem in medical care. It is said that bronchiectasis acquired in infancy (before the age of two) is a highly fatal disease, and Anspach<sup>1</sup> states that all infants die who develop it in their first year of life. Few untreated patients who acquire bronchiectasis before the age of ten live past the age of forty.<sup>2</sup> But when the disease is acquired after thirty years of age, patients live on, often without the increasing disabilities of emphysema, fibrosis and cough that may accompany chronic pulmonary infections in advancing years. It is true that bronchiectasis is the commonest cause of nontuberculous pulmonary hemorrhage in all ages,<sup>3</sup> as well as the most frequent cause of hemorrhage up to the age of twenty.<sup>4</sup> And it is known that bronchiectasis may be simply the acute clinical condition that masks an underlying bronchogenic carcinoma or pulmonary tuberculosis. This grim picture accounts for much of the aura of pessimism surrounding the medical treatment of bronchiectasis. But this point of view is not entirely justified in reviewing the natural history of this disease. For bronchiectasis may exist with few or no symptoms for many years, and long periods of well-being may be interrupted only by sporadic episodes of bronchitis. The individual constitutional factor of high resistance to infection must

be recognized as important in these cases, just as Perry and King<sup>5</sup> showed that 38 per cent of their nonsurgical patients had an "excellent living and working capacity." It should be clear that there is no stereotyped relation between the pathologic extent of bronchial dilatations and the severity of clinical symptoms. Some patients with extensive bilateral disease live normal lives with minor limitations of cough and sputum, others with so-called "dry bronchiectasis" may have recurrent hemoptyses or pulmonary hemorrhages, and fetid sputum may accompany relatively little unilobular disease. Such is the experience in the clinic at the Boston City Hospital and in private practice. This knowledge of the satisfactory progress of many cases is not entirely understood, but it is stressed to obviate the prevailing pessimism that surrounds medical care, as well as to present a fuller understanding of the long course of bronchiectasis and to substantiate a better prognosis. In the past there has been too great a tendency to group the medically treated case with the wholly untreated case of bronchiectasis into an unsatisfactory nonsurgical or so-called "medical result." The results of a surgical "cure" may be extraordinarily good, but the benefits of medical care should not be overlooked.

It is of great interest that in the Massachusetts General Hospital series of 400 cases, 59 per cent were unsuitable for surgery for one reason or another.<sup>2</sup> Alexander<sup>6</sup> also points out that in any large number of patients with bronchiectasis 50 per cent should not have excision surgery. The patients not suitable for surgery are those with too much or too little bronchiectasis, those with limited cardiovascular reserve, those with limited pulmonary reserve because of associated emphysema, those with concurrent disease and those who will not submit to surgery. Furthermore, asymptomatic bronchiectasis does not require excision.<sup>6</sup> Perry and King<sup>5</sup> also observe that when surgery has been done, follow-up studies indicate that approximately a third of patients operated on still are in poor or only fair condition, in other words, a third of the operated cases subsequently need medical treatment. In these cases residual disease remains with chronic cough, sputum and often hemoptysis that is not suitable for further surgery. Thus, it appears that about two thirds of all cases of bronchiectasis, with or without surgery, require medical supervision and care.

It is because this large number of patients will always need medical treatment that the following considerations are presented. Although the medical

\*Part of a symposium on bronchiectasis presented at the annual meetings of the Massachusetts Medical Society, Boston, May 21, 1947.  
†Instructor in medicine, Harvard Medical School; consultant on diseases of the lung, Veterans Administration.



course may be a difficult, painstaking supervision of details in daily living, a simple practical routine may suffice to maintain excellent health

### MEDICAL CARE

The medical management of bronchiectasis is directed toward mechanical drainage, the control of infection, measures to improve the general health

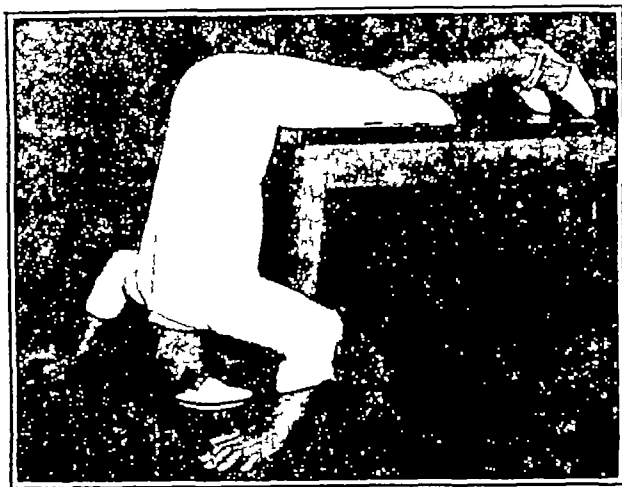


FIGURE 1 *Position of Election for Dependent Vertical Postural Drainage in Basal Bronchiectasis*

of the patient, and (as important as any factor) the prevention of the condition before it occurs

### Mechanical Drainage

The Jacksons<sup>7</sup> compare the putrefaction that gives rise to the foul odor of severe bronchiectasis to the septic tank. Early purulent exudate is often too thick and viscous for expulsion. But with stagnation and bacterial action liquefaction permits expulsion. Medical treatment is aimed at hastening this technic of nature.

Postural drainage thus becomes the most important single mechanical procedure for emptying dependent bronchiectatic cavities of their secretions. The emptying should be as complete as possible and sufficiently frequent to prevent any amount of reaccumulation. It is a treatment that must be carefully studied with each patient. Four details are essential to its proper execution.

The first is position, for postural drainage can best be carried out from a high bed or table with complete vertical dependence of the trunk, with both hands on the floor and with a basin conveniently placed for expectoration (Fig 1). Clumsiness and occasionally weakness and dizziness may accompany the first efforts at treatment, but patients soon accommodate themselves to its use so effectively that it becomes routine. For older patients and obese and dyspneic persons for whom this pro-

cedure is too difficult, it may be arranged by the use of a hinged leaf to a table. Alexander<sup>8</sup> showed that patients at work who could not find a convenient bed or table for postural drainage could, in the seclusion of a lavatory, substitute the grotesque and somewhat humorous position of flexion at the waist, with the knees slightly bent, the head far down, the buttocks as high as possible and the hands grasped behind the knees (Fig 2). This provides a fairly effective substitute form of postural drainage. Secondly, for the best results in postural drainage, the thinning of stagnant secretions becomes essential for their mechanical removal. Many shotgun expectorants are available, but the most effective are iodides, ordinary steam inhalations, ammonium chloride and creosote. Depressants with



FIGURE 2 *Substitute Position for Drainage of Basal Bronchiectasis When a High Table or Bed Is Not Available, As When at Work*

morphine derivatives should be avoided if possible, since they become habit forming in the chronic course of the disease and reduce expulsion of secretions, facilitating retention in the lung. Thirdly, bronchodilators such as adrenalin, ephedrine, Aminophylline and mucosal vasoconstrictors like Neo-Synephrine inhaled judiciously through a nebulizer with oxygen under pressure, or by a hand-bulb method, may greatly facilitate the loosening of secretions for postural drainage. And fourthly, deep expiratory and very deep inspiratory breathing before and during postural drainage may help the emptying of deep secretions. The frequency of performing postural drainage is a matter of individual trial and error. The timetable may be every two hours, or once a day, but should be often enough to keep the sacculations as free as possible from secretions. There may be long periods when drainage is unnecessary. Constant drainage cannot be carried out. Lying on the opposite side with some elevation of the foot of the bed is in no way as

effective as the vertical dependent position. Many patients, however, who produce nothing while in this position raise abundant quantities of sputum immediately on sitting upright.

An example of the value of regularity in postural drainage is provided by the case of a fifty-seven-year-old man, who was followed sporadically for ten years in the Thoracic Clinic of the Boston City Hospital for bilateral basal saccular and cylindrical bronchiectasis. He returned not long ago for check-up on a recent pneumonia controlled easily with penicillin. He was well and strong, looked ten years younger than his age and had only a morning cough and expectoration. In 1937 this man had first been seen in the Thoracic Clinic for severe recurrent hemoptyses of 30 to 180 cc of red blood off and on for two years, with cough and productive sputum. So extensive was the bronchiectasis in both lower lobes that bilateral lobectomy was advised, but refused. Consequently, the patient was schooled in the art of postural drainage and advised to use it every two hours. In time, it became unnecessary to go into position often, and for several years, with unflinching regularity, he has carried out the postural drainage once daily. Each morning he raises not more than 5 to 10 cc of thin mucopurulent material, rarely coughing again until the next day's postural drainage. The patient states that he has lived and worked without interruption because of illness.

Bronchoscopy remains an important procedure in the handling of bronchiectasis, and a necessary one in cases presented for surgery. Its need is for the removal of unsuspected foreign bodies and for the diagnosis of primary bronchogenic carcinoma, which is too often masked by bronchiectasis. The procedure is useful in segmental location of the disease within the lung and of value in aspiration treatment. Deep, widespread, careful aspiration of bronchiectatic lobes after shrinking of the mucosa occasionally has a place in the mechanical removal of secretions, but its regular routine use has been valueless.

#### *Control of Infection*

Chemotherapy in any form has so far provided no cure for bronchiectasis, but its judicious use in conjunction with mechanical drainage can make life bearable for many patients with severe bronchiectasis and can shorten the duration of the acute attacks of bronchitis and pneumonitis in milder cases.<sup>8-12</sup>

The bacteriology of bronchiectasis in its chronic phase is a composite picture of mouth organisms giving place to predominant types only during intercurrent pneumonias and infections. Both inhalation and intramuscular administration of penicillin have earned their place singly and simultaneously in the medical treatment of this disease. The purpose of inhalation is the direct application of the drug to the bronchial walls and to the secretions of the sacular dilatations. Blood levels

are much lower than those obtained by intramuscular administration. Absorption by the respiratory route alone is not adequate to take care of deep-seated pulmonary suppuration. Penicillin by inhalation should not be expected to reach deep into bronchi obstructed by thick secretions. Therefore, well executed postural drainage should precede the use of penicillin aerosol. If necessary, inhalation or injection of bronchodilators may be used with postural drainage in the first days of acute attacks.

The use of penicillin by whatever route in this chronic disease marked by exacerbations of symptoms must be considered temporary. Its value is dependent on the suppression of sensitive organisms, and its usefulness wears off in two to four weeks. The remission will last until another acute respiratory infection supervenes, unless the fundamental principles of mechanical drainage continue to be carried out regularly and with recognized effectiveness. Dependence on effectiveness of the drug without postural drainage is unwarranted.

At present, studies point toward the usefulness of sulfadiazine in daily doses of 1 gm for many months. Segal<sup>13</sup> has had success with its use in long-term medical management of bacterial control in bronchiectasis, between brief periodic uses of penicillin. But in the long-term use of sulfadiazine even non-allergic patients must be guarded carefully against sensitivities. The best results with any drug will be in patients with the most sensitive organisms and in those with the best inherent constitutional resistance to respiratory infections. Studies of bacterial flora will help, especially in the difficult case.

Intercurrent infections of virus type, like the common cold, grippé, influenza and virus pneumonias, commonly excite otherwise quiescent bronchiectasis into acute exacerbations. Inhalation of penicillin or sulfadiazine at the beginning of such infections, although known to be ineffective against the virus, has in my experience been valuable in preventing secondary invaders and serious reactivation of existing bronchiectasis.

Sinusitis has a varied influence on the symptomatic course of bronchiectasis. Goodale<sup>14</sup> has shown that there is a high incidence of sinusitis in the late years of bronchiectasis, and the more extensive the bronchiectasis, the more severe the sinus disease. Once sinusitis is acquired he believes that damage to the lungs is increased. At the same time, however, he points out that these patients are more susceptible to respiratory infections. This concept is entirely logical, for spread of sinus infection by the bronchial route is direct, and spread by lymphatic drainage is by the right side of the heart to the lungs. Sinusitis has been quite thoroughly exonerated as an etiologic factor in bronchiectasis. The influence of sinusitis on bronchiectasis and vice versa is often seen by the clearing of infection in either one followed by beneficial effects

upon the other. But sinus disease is closely linked to individual susceptibility to infection, and conservative care of sinusitis with chemotherapy deserves a trial. So too with the mouth, all infections of the teeth and gums need meticulous care.

### *Improvement of General Health and Hygiene*

Patients with bronchiectasis must learn to live with their disease and to make the adjustments that are essential to their well-being. Like the patient with valvular heart disease who must avoid competitive sports and severe exertion, the patient with bronchiectasis must protect himself against respiratory infections and take good care of those that come his way. Good nutrition is important in the control of any chronic infection. Its specificity, however, is hard to define except in the maintenance of normal body weight by a diet high in protein and vitamins in this disease in which nitrogen catabolism is elevated by chronic infection. The prevention of anemias in the presence of infection deserves serious attention. A life well regulated with rest and exercise should be so ordered as to avoid any lasting fatigue. Smoking may aggravate a respiratory mucosa already inflamed with basal infection, especially in patients sensitive to nicotine. Avoidance of exposure to cold and wet and sleeping in warm fresh air, rather than freezing cold drafty rooms, are of value to those who are sensitive to acute respiratory diseases. Change of climate to higher inland areas well away from the Eastern seaboard may contribute to the well-being of patients with more serious disease. These details—each one in itself, perhaps, unimportant—all contribute to build up the general health, which chronic infection tends to break down.

### *Prevention*

Knowledge of the cause and pathogenesis of bronchiectasis has contributed greatly to understanding of its clinical picture. The part played by atelectasis and infection from whatever cause should lay the pattern for prevention. It has been shown that 65 per cent of all cases develop in the first two decades of life<sup>2</sup> and that bronchiectasis is the leading cause of hemoptysis and pulmonary hemorrhage in that age period.<sup>3, 4</sup> Thus, two thirds of the problem of prevention is in the hands of those physicians who care for children. Lobar and lobular atelectases lay the foundation for the development of bronchial dilatations.<sup>1, 15-20</sup> Thick tenacious mucus, in the form of obstructing bronchial plugs, has been shown by Clerf<sup>21, 22</sup> to produce the clinical and x-ray signs of collapsed lobes. But infection without atelectasis may also cause bronchial dilatation by its destruction of the bronchial wall.<sup>23</sup> Probably, both atelectasis and infection conjointly are responsible etiologic factors.

Prevention thus takes two major directions. The first is early diagnosis of bacterial pneumonias, with

adequate chemotherapy. The second is re-expansion of atelectases that persist after pneumonias and acute respiratory infections, especially in children.

The unresolved pneumonias, the continued or recurrent coughs with low-grade fever and the lasting physical signs that follow acute respiratory disease may mask or may be the signs of remaining atelectasis of small bronchioles or lobules of the lung. Massive collapse is not necessarily present, and it is the smaller pulmonary segments that are revealed only by x-ray study when the acute disease is over. But for more practical purposes, deep-breathing exercises of the affected side—forced expansion of the chest hourly against the pressure of a hand placed over the pneumonic area—may be begun immediately after the acute phase has subsided. This method, described by Harkin<sup>24</sup> and used in conjunction with expectorants and postural drainage, may be sufficient to expel obstructing bronchial plugs and re-expand residual atelectases. X-ray evidence of definite collapse that does not clear with these simple measures indicates the need for bronchoscopy for aspiration of the mucous plug.

A further step in the field of prevention of bronchiectasis is the prompt removal of aspirated foreign bodies and of benign endobronchial tumors before permanent bronchial damage has occurred. The early diagnosis of lung abscess, with active chemotherapy and early surgery if necessary, should prevent the bronchiectasis that commonly follows it.

### CONCLUSIONS

A prophecy for significant reduction in the incidence of bronchiectasis in the future lies in the experience that the prevention of bronchiectasis will naturally follow the present-day treatment of pneumonias and respiratory infections of bacterial origin, especially in childhood. The medical treatment discussed above is not offered as a substitute for the case of bronchiectasis uniquely suited for excision surgery. It is offered for patients who already have the disease and are not suitable for operation or refuse it. The natural history of bronchiectasis is so varied in its course that the following factors are needed: a careful medical and surgical evaluation in each case, a period of observation when the details of mechanical drainage are studied, a time when the bacteriology and effects of chemotherapy on its control are observed, and a place where the general health and hygiene of the patient are reviewed and measures of prevention against common respiratory diseases are instituted. But especially is there need to weigh the unknown factors of constitutional resistance or susceptibility to respiratory infection when the prognosis of bronchiectasis is evaluated in each case.

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## ESOPHAGEAL STRICTURE FOLLOWING AGRANULOCYTOSIS DUE TO SULFONAMIDE THERAPY

### Report of a Case

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FALL RIVER, MASSACHUSETTS

**S**ULFONAMIDE therapy carries with it the threat of depression of the centers of blood formation and agranulocytosis and thus of agranulocytic angina. Should the process that sets up this angina extend to the esophagus, acute esophagitis results. The patient may survive the acute phases of the disease, only to face marked esophageal stenosis as a result of secondary cicatricial scarring. Investigation of the literature has revealed no reports similar to the following case of esophageal stricture resulting from agranulocytosis caused by sulfonamide therapy.

In November, 1945 a 38-year-old woman was admitted to the hospital with a peritonsillar abscess.

The past history included numerous attacks of cholecystitis and renal-tract infection. Sulfadiazine had been prescribed, except during the last attack which immediately preceded the present illness and for which she had been treated at a Boston clinic with sulfathiazole.

The present illness had begun 8 days previously with a sore throat. A physician prescribed 1 gm. of sulfadiazine every 3 hours. This regime was continued until admission. However in spite of this therapy, the patient became rapidly worse.

On admission a peritonsillar abscess was found and opened. Pus exuded from the wound. Ulcerations on the buccal mucosa gradually became fulminating and spread to the lips. The white-cell count was only 1200, all of which appeared to be lymphocytes; no young forms were found. To complicate the situation further, the blood was Rh—.

The temperature rose from 102 on admission to 105°F on the second day and then spiked between 102 and 105°F until the 7th and 8th hospital days, when it rose to 106°F.

Sulfadiazine was stopped on admission and 30,000 units of penicillin intramuscularly every 3 hours was started. The patient was supported with intravenous fluids and transfusions of compatible blood. However her condition grew steadily worse during the first 8 days. The pulse went from 120 to 140 per minute and then to 160 per minute for short periods. The quality became poor. The patient became irritable. Rales appeared in the chest and it was necessary to suction the upper air passages to keep them clear.

Dr. William F. Murphy of Boston who saw the patient in consultation expressed the opinion that the agranulocytosis

was due to the sulfonamides previously administered and that the present therapy, which included liver extract, was correct. He was encouraged by the blood smear on the 9th day, which

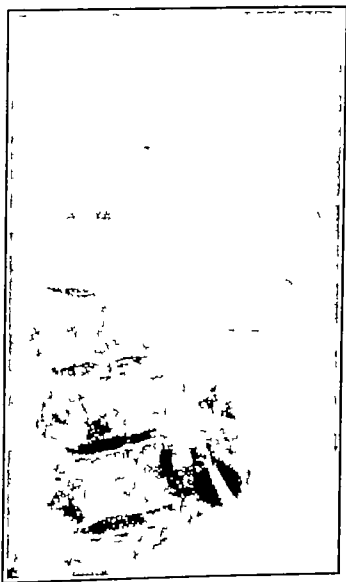


FIGURE 1. Roentgenogram Showing Esophageal Stenosis on May 1, 1946, before Passage of a Bougie.

showed a white-cell count of 3000 with young forms indicating bone-marrow activity.

By the 11th day, there was slight improvement and after the 14th day rapid clinical recovery. During the last days of

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the hospital stay a soft diet caused pain on swallowing, but at discharge on the 36th hospital day the pain had gone, although slight difficulty in swallowing remained.

At home, the patient at first gained weight and by chewing her food thoroughly swallowed without too much difficulty.



FIGURE 2 Roentgenogram Showing Esophageal Stenosis on September 12, 1946, after Passage of a No 32 Fr Bougie

However, the dysphagia progressed until May, 1946, when she could swallow only fluids or thin gruels. She had lost 10 pounds during the previous 2 months.

A barium study revealed a normal esophagus down to the level of the carina. From that point, the esophagus showed a

long, funnel-like narrowing, where the lumen was gradually reduced to 5 mm; thin barium flowed fairly readily through the involved segment, but thick barium paste met almost complete obstruction (Fig 1).

A size 9-54 Jackson esophagoscope was passed to the level of the carina, above which the lumen and mucosa appeared normal. At this point, the lumen narrowed markedly, and the mucosa was pale and lusterless. The esophagoscope was withdrawn and No 14 and 16 Fr filiform bougies were slowly passed. Moderate resistance was met.

The patient subsequently noticed slight improvement in ability to swallow. She was discharged and has returned at intervals of 2 and 3 weeks for bouginage. The size of the bougie has been slowly increased until a No 34 Fr is now used. She has gained weight and feels well. However, after 2 or 3 weeks, increasing dysphagia slowly returns. Furthermore, bougies larger than a No 34 Fr meet with marked resistance. Figure 2 demonstrates esophageal stenosis after passage of a No 32 Fr bougie.

Dr Richard H Sweet, of Boston, who examined the esophageal x-ray films, stated that after further study this patient might be a good candidate for transthoracic esophagectomy.\*

### SUMMARY

A case of marked esophageal stenosis following agranulocytosis due to sulfonamide therapy is reported.

It is assumed that the same ulcerative process that caused the severe angina of the mouth caused ulcers in the esophagus and that, after the acute esophagitis had resolved, secondary cicatricial stenosis took place.

Had the nature of the process taking place in the esophagus been appreciated sooner, bouginage at an earlier date might have prevented the resulting stenosis.

A search of the literature has failed to reveal a similar case.

151 Rock Street

\*Since this paper was submitted for publication Dr Sweet has successfully performed a transthoracic esophagectomy. The patient now swallows without difficulty. Because of the new elevated position of the stomach large meals cause mild dyspnea, but if small meals are eaten more frequently, no distress is encountered.

## THE DOCTOR AND VOCATIONAL REHABILITATION FOR CIVILIANS IN MASSACHUSETTS

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**A** OPPORTUNITY for members of the medical profession to take part in the vocational rehabilitation of handicapped civilians is presented to the private practitioner and specialist through a program administered by each state in partnership with the federal government. Recently, a pamphlet entitled *The Doctor and Vocational Rehabilitation for Civilians* was sent to all members of the American Medical Association, with a copy of a letter from Henry H. Kessler, M.D., consultant to the Office of Vocational Rehabilitation, Federal Security Agency, to inform every physician of the new services available for the assistance of handicapped patients. The Division of Vocational Rehabilitation of the Department of Education is the agency in Massachusetts by which this program is administered for the restoration of the earning capacity of the handicapped to enable them to earn their livelihood in competition with the able-bodied. The achievement of this goal for disabled civilians, who outnumber those disabled in war, rests primarily in the hands of the physicians, who are the logical case finders as well as the final purveyors of the necessary medical treatment.

Vocational Rehabilitation was established by the National Rehabilitation Act in 1920, when Congress granted financial aid to the States for disabled civilians. It was established as a public service in the same sense as the school systems, health departments and public libraries to extend vocational training to the physically handicapped. It was not until Public Law 113 was passed by Congress in 1943, amending the National Rehabilitation Act, that medical care could be provided to alleviate a condition, either physical or mental, that constitutes a vocational handicap.

To be eligible for the services of the Division of Vocational Rehabilitation, an applicant must be a resident of Massachusetts and of legal employable age (sixteen years) and must have a physical or mental disability that prevents him from obtaining employment. Any patient whom the physician regards as eligible can be referred to the Division for consideration. A report of the physician's findings and recommendations should accompany the referral.

Successful rehabilitation, which may be a long and complex process, requires the integration of professional skills at every stage. To aid him in working with the patient as a person, the physician

needs a team of skilled workers, including the nurse, medical social worker and occupational and physical therapists, as well as the vocational counselor of the Division, who knows the employment field and the facilities for training for suitable occupations for the handicapped patient. Rehabilitation should begin at the point of diagnosis, when the extent of disability may be estimated and plans formulated for the eventual return of the patient to economic usefulness. To attain this goal, each person should be evaluated from a medical, psychologic and emotional standpoint prior to selecting a vocational objective, since many factors need to be considered in helping a handicapped person select a suitable employment objective.

It is the policy of this program to compensate physicians, clinics and hospitals of the patient's choice for their care of the patient in the same manner in which it compensates the schools and colleges for tuition. A professional advisory committee, which is composed of several physicians, including a member appointed by the Massachusetts Medical Society, and members of allied professions have been appointed to advise the Division concerning physical-restoration policies and procedures. The chairman of the Committee on Rehabilitation of the Massachusetts Medical Society is the member representing the Society on the advisory committee. The professional advisory committee has approved the State plan for providing medical care and a fee schedule prepared by the Committee on Rehabilitation of the Massachusetts Medical Society. The fee schedule approximates Blue Shield fees and is in conformity with fees paid by the federal Bureau of Employees Compensation and the Massachusetts Departments of Public Health and Industrial Accidents. The fee schedule submitted by the Committee on Rehabilitation of the Massachusetts Medical Society was published in the *Journal* in the issue of December 20, 1945. This fee schedule has been approved, in condensed form, by the federal Office of Vocational Rehabilitation. Upon request, the division will gladly supply any physician with detailed information about the schedule.

Applications for vocational rehabilitation for eligible persons should be made to any office of the Division of Rehabilitation as soon as possible after the onset of the disability. Application may be made in person or by mail and by the handicapped person himself or in his behalf by a physician, hospital, social worker, employer, insurance company, fraternal or labor organization, friend or relative or

\*Director, Division of Vocational Rehabilitation, Massachusetts Department of Education.

by any interested citizen or agency. It is not necessary to use any special form or blank.

The Commonwealth is divided into districts, and a vocational counselor is assigned to a group of communities for work with applicants residing there. The administrative office is located in the Education Building, 200 Newbury Street, Boston, where the Chief Medical Consultant is available on a part-time basis for advice on physical-restoration policies and procedures and for decisions on cases to be accepted for medical and surgical treatment. District offices are located in Boston, Springfield and Lowell, with branch offices in New Bedford, Worcester and Pittsfield. Medical consultants who are attached to each district office review the medical material on each applicant, discuss his limitations for employment with the vocational counselor and decide whether the mental or physical disability is a substantial employment handicap from a medical standpoint. Further diagnostic procedures are recommended by the consultants, when indicated, for which the Division may be financially responsible without investigation of the economic need of the applicant. However, when treatment is advised, financial need for these services must be established.

An applicant may select his family physician — or any physician licensed to practice medicine in Massachusetts — for the general medical examination, which is required for all applicants. This may be paid for by the Division, according to the fee schedule. A serologic test and a urinalysis are essential parts of this examination, which is designed to give full information concerning the person's general physical condition as well as the specific disability for which he is being referred. The opinion of the doctor regarding the occupational limitations is especially important. The report form has recently been revised by the medical consultants to the federal agency and has been simplified as much as possible to save the doctor's time and still include the information necessary. If the general medical examination indicates the need of a specialist's examination, the physician is asked to recommend such a procedure, and the medical consultant of the Division will authorize an examination by a qualified specialist selected by the applicant and the physician.

Every person accepted for vocational rehabilitation by the Division receives counseling and guidance. He may receive vocational training or education in schools, on the job, by correspondence or by tutor or service for placement in the right job. All these services may be given without determination of economic need.

It is necessary, however, to determine economic need for the following services, if they are required to prepare for employment: surgical and medical treatment and psychotherapy, hospitalization, not to exceed ninety days, specialist treatment in any field, prosthetic appliances, including artificial limbs

and hearing aids, physical and occupational therapy, dental treatment, and nursing services, drugs and supplies. Instructional and training supplies, transportation and maintenance if required during rehabilitation are included.

In determining financial need, the Division recognizes that an applicant may have sufficient income to meet all ordinary living expenses but may lack a surplus to meet the cost of medical care. The program of physical-restoration services is designed to help the medically indigent, who often postpone surgery and medical care, necessary as part of a rehabilitation plan, because they are unable to pay for the service.

Eligibility for physical restoration further requires that the disability must be static, in the terms of Public Law 113. This has been interpreted to mean a disease that is relatively stable, slowly progressive or chronic but amenable to treatment. Care for acute illness may not be furnished, and this program cannot be construed to mean a general medical-care program.

The cost of rehabilitation for employment is readily justified as an actual economic gain, as shown by reports issued by the Division of Vocational Rehabilitation and the federal office. The expenses of rehabilitation are nonrecurring expenditures, whereas public assistance to a handicapped person may be a constant expense for years. Statistics show that at the time of application for rehabilitation, about a third of the applicants were not supporting themselves. Most had never worked, and rehabilitation services enabled many who were working to be more advantageously employed.

Rehabilitation through the Division can be made more effective by the collective action and assistance of individuals and organizations. Close co-operation is maintained with physicians, hospitals, schools for the handicapped as well as public and private schools, social agencies and all state departments concerned with the health and welfare of the residents of Massachusetts. The co-operation of individuals or organizations to develop employment opportunities for the handicapped is especially welcome. Teamwork is necessary in working out the details of a rehabilitation program, and most important of all for its success is the co-operation of the handicapped person himself.

The practicing physician's judgment of the physical condition of the client is the basis on which the rehabilitation plan is built. There is no substitute for this, and the support and approval of Massachusetts physicians is needed by the Division of Vocational Rehabilitation, not only in the carrying out of the rehabilitation services but also in the finding of disabled persons who may benefit by this program. A pamphlet outlining the services available may be obtained on application to any of the offices of the Division.

## MEDICAL PROGRESS

## CUTANEOUS MEDICINE (Concluded)

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## INFECTIONS

## Virus

Extensive herpetic eruptions of the lips may be serious, owing to subsequent scarring causing circumoral constriction. Herpes labialis occurs in 25 to 50 per cent of cases of cerebrospinal meningitis on the fourth or fifth day of the disease. It is probably due to the ever-present virus, being activated by febrile illness.

Toward the close of the nineteenth century a complication of infantile eczema characterized by a so-called "varicelliform eruption" was first described by Kaposi<sup>138</sup> as an acute outbreak of numerous vesicles, partly scattered and partly arranged in groups. The vesicles are as large as lentils and are filled with clear serum, and the majority are umbilicated. The largest number of vesicles are found on already eczematous skin, smaller groups appear on previously intact skin. The patients have a high fever and are extremely restless.

A recent paper of Lane and Herold<sup>137</sup> has done much to make secure the position of this disease as a separate entity. Barton and Brunsting<sup>135</sup> also treat the condition as a separate disease. King<sup>139</sup> considers it a complication of atopic eczema—a conclusion reached through investigation of the herpes simplex virus. Ronchese<sup>140</sup> suggests the vaccinia virus as the responsible agent.

There seem to be four features that characterize the disease: an antecedent skin disease, usually atopic dermatitis<sup>141, 142</sup>; systemic involvement, shown by lymphadenitis, fever, malaise and edema, lentil-sized, umbilicated vesicopustules, discrete or in groups on a bright erythematous base, and limited almost exclusively to the sites of existing skin disease, which crust and break, new ones appearing for seven to ten days, and very slight scarring.

Wenner<sup>143</sup> has identified the herpes simplex virus in 3 cases by methods that leave no room for doubt. Blattner, Heys and Harrison<sup>144</sup> have proved the herpes simplex virus to be present and have grown it in eggs and mice. Barton and Brunsting<sup>135</sup> list the complications as stiff neck, headache, epigastric pain and incontinence of urine and feces, all of which were seen in their cases, and also hemorrhagic diarrhea, anuria, otitis media, purulent rhinitis, conjunctivitis, tetanic spasticity, corneal ulcer, gan-

grenous slough, abscess and suppurative nodes. The virus of herpes simplex, which may cause encephalitis, has been isolated from the glycerinated brain material in 2 cases of fatal encephalitis.<sup>145</sup>

Pregnancy may be complicated by various herpetic eruptions. The most serious type is herpes gestationis, which is characterized by pruritic, vesicular eruptions often mistaken for scabies. Bullous lesions may also occur, so that the eruption is often mistaken for pemphigus.

A report of 144 cases of a newly recognized rickettsial disease, so-called "rickettsialpox," in a housing development in New York merits renewed attention for its value in differential diagnosis. The agent was isolated from mites and was named *Rickettsia akari*.<sup>146</sup> The disease is characterized by an abrupt onset of chills, fever, sweats and backache, followed after several days by a rash. About a week prior to the onset of the fever there is an initial lesion, variously described by the patients as a pimple, boil, blind boil or insect bite. The initial lesion is a more or less round, red papule, firm to the touch. The papule enlarges and the center becomes vesiculated. Ultimately it shrinks and dries, and a black eschar forms. In the fully developed state the lesion frequently resembles certain stages of vaccinia. Regional lymph nodes are usually enlarged and sometimes slightly tender to the touch. The initial lesion persists for approximately three weeks and usually leaves a small scar. A rash appeared in all the New York cases, usually at the onset of the fever or a day or two later. In some cases it was first seen on the arms or legs, in others, it appeared on the abdomen, back, chest or face. In 2 cases lesions occurred on the mucous membranes, in 1 on the palate and in 1 on the tip of the tongue. In no case was the rash observed on the palms or soles.<sup>147</sup>

Interest in herpes zoster has been renewed by the suggestion of surgical section of the involved nerve or of several segments to relieve the persistent pain of post-zoster neuralgia. This is required in rare cases, but most patients respond to simpler methods of treatment.

Geniculate zoster (the Ramsay-Hunt syndrome) with involvement of the cranial nerves is interestingly described by Tschiasny,<sup>148</sup> who localized the lesion by the subjective and objective findings.

A virus may be the etiologic factor in conditions such as Behcet's disease. Ten years ago Behcet

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established as a clinicopathological entity a recurrent triad of symptoms. Characteristic of this syndrome are recurrent ulcerations of the oral cavity and genitals and repeated attacks of uveitis, which in later stages is associated with hypopyon.<sup>167-169</sup> The eye involvement may precede, coincide with or follow the oral and genital manifestations. The ulcers of the mouth and genitals are small and discrete, either aphtha-like or nodular and necrotic. Thomas<sup>170</sup> describes a case that he thinks is the first to be reported in Great Britain.

Thirty-three cases of erythema bullosum malignans of the pluriorificial type occurred at the Willard Parker Hospital for Contagious Diseases between 1932 and 1946, with a mortality of 18 per cent. The most urgent feature requiring immediate and constant ophthalmologic care was the destructive lesions of the cornea and conjunctivas terminating in grave ocular sequelae—panophthalmitis and blindness. An upper respiratory onset occurred in over half the patients, and vaginal and urethral stenosis in 2 cases. The treatment is symptomatic in this disease, in which a virus is suspected as the causative factor. Penicillin administered in 2 recent cases materially aided recovery.<sup>171</sup>

In 1922 a "new eruptive fever associated with stomatitis and ophthalmia" was reported by Stevens and Johnson.<sup>172</sup> This disease is characterized by an acute, sometimes fulminating systemic reaction, with fever and prostration, erythematous generalized skin rash and severe stomatitis, followed by sloughing. With occasional exceptions<sup>173</sup> the conjunctivas are involved. The usual period before resolution of the skin lesions is three weeks.<sup>174</sup> The exact appearance of the lesions varies somewhat in different cases, and Stevens and Johnson even repudiated as inadequate the diagnosis of erythema multiforme.<sup>175</sup> Although this disease has been considered primarily pediatric, approximately a third of the cases reported since 1922 have occurred in patients over fifteen years of age,<sup>176-180</sup> the case reported by Jones et al.<sup>180</sup> having occurred in a fifty-six-year-old woman. A case with an erythematous skin eruption associated with fever, a purulent conjunctivitis, severe stomatitis and balanitis is reported by Patz.<sup>181</sup> Corneal ulceration with opacification was the only sequela. The course and clinical picture were almost identical with those in the cases described by Stevens and Johnson.

### *Bacteria*

In children the exanthemas of scarlet fever, measles and rubella are readily recognized owing to age expectancy, but in adults they are frequently mistaken for other diseases. Unless a disease is endemic or epidemic, recognition of an infectious or contagious disease by its cutaneous manifestations alone is difficult. The rose spots of typhus and typhoid fever may be similar. In the former, however, these spots change to petechiae, the so-called

"mulberry rash." Petechiae often have a diagnostic and prognostic value.

Twenty years ago Hurxthal<sup>182</sup> described the skin manifestations of subacute bacterial endocarditis and stated that petechiae are found in 50 per cent of cases, conjunctival lesions are most reliable. Small, red or pinkish, cutaneous macules due to emboli and ranging from 2 to 4 mm in diameter are often found on the inside of the palms and on the fingers, soles and toes. These first blanch on pressure, but later may or may not, they clear, leaving areas of fawn-colored pigmentation. Osler nodes are also present, especially at the tips of the fingers and toes, and consist of tender cutaneous nodes. Other lesions, such as purpura, deep tender erythematous nodules and various skin rashes, have been reported. Embolic plugs or hemorrhages of the retinal vessels are common. Osler nodes or conjunctival lesions may be indicative of bacterial endocarditis.<sup>182</sup>

Jones and Tichy<sup>183</sup> state that a special search should be made for petechiae, Osler nodes, Janeway lesions, splinter hemorrhages beneath the nails and glossiness of the rim of the skin at the nail bases, indicative of early clubbing of the fingers,<sup>182</sup> splenomegaly and changes in the heart murmur. They report 9 cases in which penicillin sterilized the blood in 7.

In the last few years there has been an increase in the number of cases of anthrax in Massachusetts, therefore, physicians should be on the alert for early diagnosis and the rapid institution of penicillin, which is apparently of great value in the control of this disease. From 1940 to 1945 there were 21 cases, with 7 deaths—a mortality of 33 per cent.<sup>184</sup> Furthermore, it appears that the majority of deaths can be avoided if the disease is recognized at an early date and penicillin therapy is immediately instituted.<sup>184-186</sup>

A report of 25 cases by Ellingson et al.,<sup>187</sup> with uneventful recovery, recommends the use of penicillin. Their description of the initial lesion is well worth repeating. The earliest visible sign is a small, red macule that becomes elevated to form a firm, red papule. Within a few hours there appears a central vesicle filled with clear or opalescent fluid in which organisms can be demonstrated by smears and cultures. The vesicle may rupture early, leaving a small ulcer or may enlarge by direct extension or by development of a ring of satellite vesicles. A zone of deep-red indurated tissue 2 to 3 mm wide surrounds the vesicles and in turn is surrounded by a zone of erythema 5 to 20 mm wide, fading toward the periphery. Edema about the lesion may be present. A striking feature of the infection is the absence of pain in the lesion itself, which is in sharp contrast to abscesses caused by the common pyogenic organisms. Enlarged regional lymph nodes, however, may be acutely tender during the development of the anthrax lesion.

*Pseudomonas aeruginosa* infection may be accompanied by various cutaneous eruptions. Stanley<sup>183</sup> states that prominent among the signs of pyocyanous sepsis are skin lesions that begin as macules or vesicles and later become bullous or often pustular. When the surface epithelium is denuded from the lesions and the center sloughs out, a characteristic ulcerated gangrenous area is produced. This was first described by Barker<sup>184</sup> in 1897 and was later named "ecthyma gangrenosum" by Hitschmann and Kreibich.<sup>185</sup> Detailed descriptions of ecthyma of this type were given by Fraenkel<sup>186</sup> in his classic paper written in 1917. It is most frequently encountered in the anogenital region, and also in the axillae, the inner aspects of the thighs and the abdomen, particularly in children. The organism is easily cultured in abundance from these areas of gangrenous skin. The necrosis may penetrate through the skin and subcutaneous tissue to the underlying muscle. Other lesions of the skin seen during the course of bacteremia include the roseola occurring in cases of so-called "Shanghai fever" described by Dold.<sup>187, 188</sup> Erythema nodosum,<sup>189, 190</sup> erythema multiforme and butterfly lesions of the face<sup>191</sup> resembling lupus erythematosus have also been described during the course of systemic infections with *Ps. aeruginosa*.<sup>188</sup>

Stanley believes that the characteristic lesions are ulcerating gangrenous areas on the skin (ecthyma gangrenosum), particularly in the perianal and axillary regions, which were exhibited in 3 of his cases. One of them showed an acute exacerbation of chronic disseminated lupus erythematosus. At the time I saw this patient he had a superimposed eruption resembling an erythema multiforme bullousum of the Stevens-Johnson type.

In treatment the sulfonamides and streptomycin are the agents of choice. A most important point emphasized in Stanley's paper is his statement that sepsis and other serious infections due to this organism are definitely rare. However, because of the widespread use of penicillin, which efficiently removes gram-positive organisms but apparently promotes uninhibited growth of this and other gram-negative bacilli, the incidence of such important infections seems to be increasing.<sup>187</sup>

Illness due to *Brucella melitensis* infection may be associated with a rash, nosebleed, glandular swellings and nasal ulcerations. The rash, macular in character, resembles that seen in streptococcal septicemia, the glandular swellings may simulate those of Hodgkin's disease. In a report of 20 cases in Iowa, Jordan and Bortz<sup>192</sup> state that the illness was characterized by fever, chills or chilliness, sweating, weakness, loss of weight, headache, muscular pains and leg pains. Although the course was mild in several cases, infection was generally severer than that caused by *Br. abortus*.

Meningococcal meningitis, also known as spotted fever or cerebrospinal fever, is apparently more

prevalent during wartime than at other times. Recognition of the rash is extremely helpful.

Osborne et al.<sup>193</sup> give a clear description of the evolution of the exanthema. In 59 cases (82 per cent) a rash was observed on admission. The skin eruption was purpuric, resembling the so-called "fleabite." These petechial hemorrhages occurred early in the course of the disease and in many cases multiplied rapidly within a short time on the arms and legs, especially about the ankles. Characteristic petechial hemorrhages occurred in the mucous membranes of the mouth and eyes and also on the palms and soles. This fact was helpful in diagnosing the disease in Negroes, whose skin is lighter on the palms and soles than on the rest of the body, making the eruption easy to detect. The organisms can be cultured from these spots and can also be directly visualized by the technic outlined by Tompkins.<sup>98</sup> There has been some speculation why the meningococcus has a predilection for the skin and—in the Waterhouse-Friderichsen syndrome—the adrenal glands. Sacke<sup>194</sup> thinks that the meningococcus has an ectodermal tropism that accounts for this. The Waterhouse-Friderichsen syndrome is characterized by the fulminating onset of a petechial or purpuric skin eruption, a peculiar dyspnea and cyanosis and profound peripheral circulatory collapse.<sup>195, 99</sup>

In the last few years the Waterhouse-Friderichsen syndrome has been reported in adults. Formerly it was thought that the disease was limited to children between the ages of two months and two years, occurring rarely in patients over nine years of age. Until February, 1943, there were only 103 cases reported in the literature, and among these only 3 patients recovered. Peabody<sup>200</sup> reports a recovery in an adult who suffered from such enlargement of the petechial spots that she developed deep pressure sores. Two reports stress the value of adrenocortical hormone in treatment.<sup>91, 95</sup>

Hill and Kinney<sup>201</sup> present an excellent clinical and pathological study of the cutaneous lesions in acute meningococcemia based on 5 cases. The presence of a skin rash has always been recognized as one of the earliest and most reliable clinical signs in meningococcemia, a fact that has led clinicians in the past to employ such titles as "malignant purpuric fever," "petechial fever," "black fever" and "spotted fever" for these infections. Concomitantly with the stage of bacteremia, or at various intervals thereafter, the meningococci metastasized to the skin, eyes, joints, heart, adrenal glands or meninges, producing various clinical syndromes. The onset and course varied widely, and the cutaneous patterns included erythematous macules, papules, nodules, vesicles and petechial and purpuric lesions. In some of Hill and Kinney's cases lesions similar to those of erythema nodosum appeared on the lower extremities and were indistinguishable from the type encountered in other

diseases In none of these cases was purpura found alone, but in every case in which it occurred it was associated with petechiae Necrosis and sloughing of purpuric lesions and gangrene of the extremities occurred in 2 patients who recovered

The sequence of events in the pathogenesis of the lesions is the localization of the meningococci in the endothelium, followed by endothelial damage and inflammation of the vessel walls, with resultant necrosis and thrombosis These changes, by permitting the extravasation of red cells, account for the hemorrhagic cutaneous lesions In all cases studied in which the skin manifestations were severe, thrombi were a striking and invariable finding They were composed largely of platelets that were attracted to the damaged endothelial linings In 2 cases in which purpura was a striking feature, the blood platelets were greatly reduced Thrombocytopenia is known to occur in many of the severe febrile illnesses, such as septicemia, typhoid fever, typhus fever, scarlet fever and miliary tuberculosis, and it is not unlikely that the fever is also a factor in the reduction of the platelets in this group of cases Vascular lesions were not restricted to the skin Petechiae and hemorrhagic manifestations were found over the serous surfaces and in the mediastinum, epicardium, endocardium, lungs, liver, kidneys, adrenal glands, intestines and spleen The vascular lesions were similar to those in the skin In other words, the skin lesions are but one manifestation of a generalized pathologic process<sup>206</sup>

Tuberculosis of the skin is fortunately rare in this part of the country Because of the frequency of pulmonary tuberculosis, however, internists are always on the lookout for the cutaneous manifestations Floyd et al<sup>207</sup> conducted interesting experiments by superimposing cutaneous tuberculosis in the guinea pig with pulmonary tuberculosis They discovered that it had a distinctly modifying effect on the disease in the lung through the response of the liver to infection This study was based on clinical work done on the subject of immunity or resistance to phthisis resulting from accidental or deliberate involvement of the epidermis with the tubercle bacillus Among certain observers it has long been an axiom that whenever lupus is present pulmonary tuberculosis rarely occurs subsequently, when it was acquired in a case of pre-existing pulmonary tuberculosis, the course of the disease was materially modified<sup>207</sup>

A recent classification by Cipollaro<sup>208</sup> of the cutaneous lesions found in tuberculosis divides these manifestations into a localized tuberculosis and hematogenous types Among the latter he includes sarcoids The difference in clinical and histologic characteristics can be accounted for by the differences in susceptibility, allergy, virulence of organisms, environmental factors and the like Whether sarcoid should be included under tuberculosis is questionable The etiology and pathogenesis of

sarcoid are not known, and its relation to tuberculosis is not established Frequently these patients are admitted to sanatoriums or exposed to tuberculosis and in this way acquire the disease

### *Fungi*

Smith<sup>209</sup> presents an excellent review of fungous infections encountered in general hospital practice—I might add, provided the hospital has a trained mycologist His illustrations are remarkable He discusses the deep mycoses, including histoplasmosis, which has caught the imagination of the medical world Darling's<sup>210</sup> original cases were characterized by fever, emaciation, anemia, leukopenia, splenomegaly and hepatomegaly More than 50 cases of histoplasmosis have been recorded in the literature, and Schlumberger and Service<sup>211</sup> report a case with autopsy in a nine-and-a-half-week-old baby Thomas and Mitchell<sup>212</sup> report a case presenting on first impression a syndrome resembling acute adrenocortical insufficiency and later that of a generalized fungous infection, presumably blastomycosis, that was demonstrated ante mortem by material obtained from biopsy to be one of histoplasmosis The patient presented extensive and generalized embolic cutaneous papular lesions

### SARCOIDOSIS

In recent years internists, roentgenologists and pathologists have become deeply interested in such entities as disseminated lupus erythematosus, scleroderma, dermatomyositis and polyarteritis nodosa Although clinically they are distinct, attempts have been made to establish a common pathological denominator<sup>213</sup> The first three are definite cutaneous diseases with a characteristic dermatologic pattern Sclerodermal changes of the heart and lungs evidenced by roentgen-ray examination and autopsy are reported<sup>214</sup> A pathologist stated that he could diagnose scleroderma from a section of the heart, but admitted that a sclerosed cutaneous patch might be confirmatory

Apparently, no such cutaneous confirmation is necessary for disseminated lupus erythematosus or sarcoidosis To students of sarcoidosis the testimony on questionable cases of industrial pneumonitis is interesting but confusing The review of Higgins<sup>215</sup> is worthy of study In an article on pulmonary sarcoidosis he reports that in four years as an industrial physician he had met with 35 cases, with 3 deaths The first and most noticeable symptom was shortness of breath, cyanosis and clubbing of the fingers and toes might or might not be present Skin lesions occurring on the fingers, the front of the thighs and the shins were noted in 5 cases These lesions were similar to papulonecrotic tuberculids By microscopical examination they were diagnosed as typical sarcoids X-ray films were suggestive of silicosis Those of the chest showed a diffuse granularity and nodulation throughout the entire

lung fields. There was no enlargement of the lymph nodes. Bacteriologic study revealed acid-fast bacteria in 8 or 10 cases.

All but 2 of the 35 patients had been engaged in the manufacture of fluorescent mercury-vapor lamps.

According to Higgins the disease does not fit in exactly with the usual conception of Boeck's sarcoid, in which most patients recover. There is considerable evidence that one is dealing with an infection in the first place, the lesion is similar in nature to tuberculosis, secondly, the disease appears three or four years after the last exposure, lastly, it was possible to identify the same bacterium in several cases, although its pathogenicity has not yet been proved. The possibility of a carrier arises.

The phosphors in most general use were zinc beryllium manganese silicate, magnesium tungstate, magnesium silicate, zinc orthosilicate (willemite), cadmium borate and lead fluoride. These powders were processed in a plant of the company in another state, where 2 cases of sarcoidosis were found. One occurred two years after exposure to fluorescent powder. Most attention among the phosphors has been directed toward zinc beryllium manganese silicate and especially to its beryllium component. It is made by mixing of beryllium oxide, manganese oxide, zinc oxide and silicic acid. About the time the first of the sarcoidosis cases were seen there were 5 definite cases of acute chemical pneumonitis in employees who had been using zinc beryllium manganese silicate, but not in the plants where the patients mentioned above worked. These persons had had considerable exposure to the dust of this phosphor.

At about the same time there were reports of a number of cases of severe acute chemical pneumonitis in plants where beryllium processing was being done. The evidence in these cases indicates that the pneumonitis was due not to beryllium but to hydrofluoric acid or sulfur trioxide, which were released into the atmosphere during processing. This acute pneumonitis is clinically and roentgenologically a distinctly different entity from sarcoid. Chemical analysis of the lungs of the patients who had died did show some beryllium present.

In summary, Higgins<sup>21</sup> states

It may be said that there is considerable circumstantial evidence that beryllium is the responsible agent in the causation of sarcoidosis by reason of the association of sarcoid cases in industries using beryllium. However there is still lacking proof that beryllium or its compounds will cause lesions similar to the sarcoid lesions found in the 35 patients described. The prolonged waiting period is not in keeping with the usual behavior of the acute phases of chemical poisoning.

Beryllium poisoning, a recognized entity, is an industrial disease that demands attention because of the loss of manpower and the fatalities incident

to increased production in the beryllium industry. During the last four years 170 cases of poisoning were seen among workers in three plants producing beryllium and its compounds and alloys. The manifestations included dermatitis, chronic skin ulcer and inflammatory changes in the respiratory tract and skin and respiratory changes, occurring concurrently or singly. The severest manifestation was diffuse pneumonitis, which caused the death of 5 patients. Experiments conducted by Hyalop and his associates<sup>22</sup> showed that several beryllium compounds are toxic to animals. Both pneumonitis and dermatitis were produced experimentally.

Marradi Fabroni<sup>23</sup> coined the term "berylliosis" for this pathologic condition. The ulcers occur on the exposed parts, particularly the forearms and hands, and are discrete and as a rule single. They cause little distress unless they become infected or are located near a joint and thus subjected to the trauma of motion. Treatment comprises early incision of the papule and curettage of the fibrous base. This center consists of caseous material within which the beryllium crystal can usually be identified. Healing does not take place until the embedded crystal is eliminated.<sup>24</sup>

Harrell<sup>25</sup> gives a clear description of generalized sarcoidosis, but the dermatologic picture varies from that of Boeck,<sup>26</sup> who describes a symmetrical eruption consisting of nodules on the head and the extensor surfaces of the skin. They ranged in size from a hemp seed to a bean, and the larger lesions had irregular contours. The lesions involved the skin and were movable with it. At first bright red, they became darker and finally assumed a yellowish or brown color. Slight scaling occurred in the older lesions. There was an increase of lymph nodes and leukocytes.<sup>27</sup> Harrell states that the clinical picture is one of a generalized disease that is most easily recognized in the skin and lymph nodes. The symptoms are those recognized in any chronic disease of low virulence and are not specific. Lesions are found by x-ray examination in the lung fields in most cases. These are usually of three types: peribronchial fibrosis or thickening, usually extending downward symmetrically into the lower lobes, symmetrical infiltration in the midlung fields, sparing the apices, and areas resembling miliary tuberculosis with a fine marbled or reticulated appearance. Eosinophils are usually present at some time and may reach 15 to 30 per cent.<sup>28</sup> Another type of x-ray appearance is that of diffuse and confluent infiltrations, which may represent a transition from other forms of sarcoidosis and may easily simulate, if not actually develop into, tuberculosis.<sup>29</sup>

Sarcoidosis can be fatal. Nickerson<sup>30</sup> reports that in 6 cases in which autopsies were made, the typical histologic picture of sarcoid was found in the viscera. In 1 case the patient undoubtedly died of sarcoid in a fulminating form. The other cases were examples of incidental sarcoid, the patients dying of

some major disease Nickerson reported lesions in the myocardium, endocardium, pancreas, testis and vertebral and femoral marrow for the first time. A varying amount of collagen was noted in each case. It was minimal in the case in which death was apparently due to the disease, and it is suggested that an increase in the amount of collagen indicates a healing reaction.

On the theory that sarcoid, like lymphogranuloma inguinale, is a virus and that, as with the latter, an antigen could be prepared from infected material for diagnostic use, the following work was done by Williams and Nickerson.<sup>223</sup> A sarcoid lesion of the skin, 2 cm in diameter, was removed. A portion of the tissue was taken for microscopical study, and the remainder was ground with the aid of sterile sand. To this, physiologic saline solution was added in a volume equal to six times that of tissue. This preparation was then sterilized by heating to 60°C for two hours on two consecutive days. Aerobic and anaerobic cultures were negative at the end of forty-eight hours. In each of the following cases stained sections and animals inoculated with the tissue removed were negative for tuberculosis. The patients showed no evidence of tuberculous infection on clinical examination, cutaneous tests or x-ray examination. The authors summarized their work by stating that 4 cases with clinical and pathological evidence of sarcoid gave skin reactions following the intradermal injection of an antigen made from a sarcoid lesion of the skin. Four normal subjects gave no such reaction. The results suggested that sarcoid is a virus disease and that it is possible to prepare a diagnostic antigen.

Several years later Kveim,<sup>224</sup> unaware of the report of Williams and Nickerson, announced the Kveim reaction for Boeck's sarcoid. After Kveim's first account of a new and specific cutaneous reaction for this disease, further investigations were carried on by Danbolt<sup>225</sup> and by others in the Scandinavian countries. Investigations indicate that the Kveim reaction is an allergic cutaneous one specific for Boeck's sarcoid. A test was made on 104 subjects, 36 of whom had Boeck's sarcoid. A positive Kveim reaction appeared in most patients in the course of the two first weeks after the antigen had been injected. A positive reaction as a rule remains positive for many months. Whereas Kveim's reaction was positive in 34 of 36 cases of definite Boeck's sarcoid, it was negative in all 64 cases that showed no symptoms of this disease. A positive Kveim reaction is a valuable support to the diagnosis of Boeck's sarcoid.<sup>224, 225</sup>

Pautrier<sup>226</sup> proposed the name of "disease of Besnier-Boeck-Schaumann" to designate a benign and chronic disease, perhaps tuberculous, which reveals itself in cutaneous, ocular, respiratory, lymphatic and osseous manifestations. He associated with the disease of Besnier-Boeck-Schaumann an affection known to ophthalmologists as the

syndrome of Heerfordt.<sup>226, 227</sup> It consists of endochoroiditis associated with bilateral parotitis, peripheral facial paralysis, recurrent paralysis and often cutaneous manifestations. Lastly, some cases of granular conjunctivitis of Parinaud are undoubtedly associated with Besnier-Boeck-Schaumann disease.<sup>228</sup> This disease, extremely variable in its clinical forms and in its evolutionary methods, usually manifests itself by persistent but not pronounced signs, reaching the eyes, the respiratory apparatus, the skeleton, the lymphoid organs, several glands, such as the parotids, and the spleen, liver and kidneys. But the favorite site is the skin, where it reveals itself by several lesions belonging to the groups of sarcoids.<sup>229-231</sup>

Longcope<sup>232, 233</sup> reported that in 11 of his 30 cases of sarcoid eosinophils comprised 6 to 35 per cent of the leukocyte count. During the active phase of the disease the sedimentation rate was sometimes elevated. A noticeable alteration of the plasma proteins was observed, there was an unusual increase in the globulin fraction, often resulting in a definite elevation of the total plasma proteins, even though plasma albumin showed normal or subnormal values.

A review of the literature on sarcoidosis for the last three years reveals no new developments or theories concerning its etiology or treatment. In April, 1944, Reisner<sup>234</sup> reviewed 35 cases. Thirty of these patients were Negroes. The age distribution was eight to over forty years. A study of 15 cases by Thomas<sup>235</sup> in 1943 revealed similar findings. Twelve patients were Negroes, and 13 were females. In all cases there was involvement of several organs, including the skin, lymph nodes, lungs, spleen and liver. The period of observation varied between one and seven years.

Dermatologists have long recognized the systemic manifestations of sarcoid. They realize that the sum total of clinical and pathological findings will determine the diagnosis, not a single finding such as that provided by x-ray study or biopsy. An interesting discussion on chronic granulomas shows the difficulty of diagnosing these conditions without extensive laboratory studies.<sup>236</sup> Included is a case report of a sixty-five-year-old man originally presenting an eruption so nondescript that a dermatologist made a diagnosis of scabies. Later, the patient showed definite nodular lesions on the lower legs. These progressed to pustulation and ulceration, with systemic disturbances that resulted in a fatal ending. The final anatomic diagnosis was tuberculosis of the skin, lungs, liver and spleen.

#### LUPUS ERYTHEMATOSUS

Over a hundred years ago, in 1841, Cazenave studied an entity previously described by Bielt and gave it the name "lupus erythematosus." Appearing usually on the face, the red elevated, well defined, scaly and atrophic patches of the discoid type of lupus erythematosus are disfiguring

This is especially true in the late stage, owing to atrophy, dirty scaling, stippling and telangiectasia. The disease arouses little interest in the physician because of lack of systemic manifestations. One might believe it to be entirely distinct from disseminated lupus erythematosus if stimulation from sunlight or irritating local or intravenous therapy, such as that with gold, did not frequently transform the local lupus erythematosus to a disseminated type with vascular and nephritic disturbances.

Acute lupus erythematosus disseminatus is a definite clinical entity, with erythematous patches on the face, hands, toes and frequently other areas of the skin. Occasionally, a multiform eruption with bullae, vesicles, purpura and generalized telangiectasia appears. The first attack may be mild, but there are usually a septic temperature, pains in the joints and muscles, lymph-node enlargement, gastrointestinal disturbances and prostration. Anemia, leukopenia and albuminuria are frequent complications. The Libman-Sacks syndrome presents a symptom complex of a septic fever, arthritis, polyserositis, leukopenia, increased globulin, renal disease and verrucous endocarditis. The cutaneous lesions are superficial and vascular. Most cases occur among young women, although an occasional man is affected.

Dine and Wilson<sup>27</sup> report a case of disseminated lupus erythematosus in a man with a clinical course of seventeen months. Autopsy revealed thickened serous surfaces, small endocardial vegetations of the Libman-Sacks type and collagenic changes throughout the body involving blood vessels, muscles, serous membranes and the endocardium. Kidney sections showed "hyaline thrombi" with a few "wire-loop" lesions of the glomeruli.

Overexposure to sunlight or ultraviolet radiation preceded the onset in a few of my patients. Other cases have followed a focal infection or an attempt to remove one, such as tonsillectomy or the extraction of an infected tooth. Fox<sup>28</sup> suggests allergy as a factor, after citing a case following the injection of horse serum.

In this country little or no etiologic significance is attributed to the rare association of this disease with tuberculosis, but some European observers still adhere to the relation between these two conditions. The diagnosis of Libman-Sacks syndrome without cutaneous manifestations is becoming too popular. Without an erythematous eruption one should be careful in making a diagnosis of lupus erythematosus disseminatus.

I am inclined to agree with Wesselhoeft and Weinstein<sup>29</sup> in rejecting the Dick's resurrection of the term "scarlatinae sine eruptione" for lupus erythematosus. Without the rash there is no scarlet fever, even though the patient is infected with a streptococcus that is causing a rash in other patients. To include all infections of the toxin-producing streptococci as scarlet fever is a misuse of the term,

since the resistance of the host is an equally important factor.

In a patient whose condition had been wrongly diagnosed as lupus erythematosus owing to x-ray findings, without an eruption, after two weeks' hospitalization without infectious precautions, a diagnosis of tuberculosis was finally made after a sputum examination showed numerous tubercle bacilli.

An interesting discussion on the diagnosis of lupus erythematosus disseminatus in a nine-year-old Negro admitted to a hospital because of cervical and axillary lymphadenopathy, but no eruption, has been presented.<sup>30</sup> The pathologist was unable to refute this diagnosis at autopsy. Klemperer<sup>31</sup> states that this disease rarely occurs in children. The patient under discussion had a white-cell count of 22,000.

The pathology of acute disseminated lupus erythematosus has been a subject of controversy. Klemperer et al.<sup>31</sup> believe that the thesis formerly advanced — that lupus is fundamentally a diffuse vascular disease<sup>32</sup> — is no longer tenable. They present evidence that the basic pathological lesion is a characteristic type of focal connective-tissue degeneration, with all elements taking part in the reaction. Inflammatory reaction, although variable, is nonspecific in type and relatively inconspicuous, and in their words "the alternative phase of the process is far out of proportion to the exudative."<sup>33</sup>

#### SCLEROSSES

O'Leary<sup>34</sup> classified the dermatoscleroses as a group of diseases that have certain features in common and for that very reason present difficulties in diagnoses. These include scleroderma, scleredema adultorum, acrosclerosis and dermatomyositis. A diffuse collagen disturbance has been suggested as a basis for the resemblance of certain of these diseases to each other. They resemble each other because of the solid edema and sclerosis of the skin.

In scleroderma death is due to diffuse involvement of the viscera. Lindsay et al.<sup>35</sup> describe the lesions of the esophagus. In the early stages there is inability to swallow more than a few mouthfuls of liquid, especially while the patient is lying down, a sense of fullness behind the sternum and a burning sensation an hour after eating that is worse when the patient is lying down at night. Fluoroscopy shows a localized narrowing of the esophagus 10 to 12 cm. above the level of the diaphragm, measuring 5 to 8 cm. in length. Dostrovsky<sup>36</sup> reports 3 cases of progressive scleroderma, all presenting acrosclerotic symptoms. Varying degrees of roentgenologically identified lesions of the lungs of a sclerotic nature are described. In 2 of the cases, fibrous and cystic changes of the lungs of a sclerodermal nature were found at autopsy.

Acrosclerosis is characterized by hardening of the skin and vasospasm of the extremities. The course is fairly benign, the prognosis regarding life and physical activity is better than that in scleroderma.

Scleredema adultorum follows an acute respiratory-tract infection, with edema of the face or upper part of the chest. The disease heals spontaneously. Vallee<sup>246</sup> reports 4 interesting cases following febrile diseases. He shows that scleredema adultorum is found in children and adolescents and that it is a systemic disease, characterized by firm, nonpitting edema affecting usually the face, neck, scalp, conjunctivas, thorax, occasionally the arms and, more rarely, the legs, it spares the hands and feet. Pleural effusions, pericardial effusions and hydrarthroses also occur, the former being localized. The electrocardiogram shows low voltage of the QRS complexes. When the disease involves the face differentiation from dermatomyositis is difficult. Muscle pain, fever, a high sedimentation rate and the widespread erythematous skin lesions occasionally seen in dermatomyositis, as well as the weakness and atrophy that are constant features of the latter disease, are not encountered in scleredema.<sup>246</sup>

In dermatomyositis the muscles of the shoulder girdle, neck and arms are the most vulnerable of the entire body once the disease has started. Jager and Grossman<sup>247</sup> believe that in general the histologic changes in the muscle are nonspecific for dermatomyositis. Keil<sup>248, 249</sup> has described what he calls the dermatomyositic facies, which he regards as consisting of two elements: definitely swollen eyelids with narrowing of either one or both lid spaces, together with a degree of edematous involvement of the adjacent portions of the cheeks and nose, and a background of faint, rosy or pale-blue skin (some call it wine-colored), the net effect is to create a sort of heliotropic bloating of the face resembling the earlier stages of cadaveric decomposition. Little is known of the exciting agent of dermatomyositis. At the present time it is prudent to accept the broad hypothesis that the various manifestations of this disease are caused by various bacterial factors.<sup>250</sup>

Periarteritis nodosa is a usually fatal disease of alleged infectious etiology, involving the smaller arteries. Various types of subcutaneous nodules and cutaneous lesions are seen in about 40 per cent of cases. Cutaneous lesions vary from purpura and petechial hemorrhages to areas of necrosis. The veins are involved in a lesser degree. The pathological picture presents a necrotizing inflammation of the lining of the arteries with a pleomorphic infiltrate and resulting injury to the wall of the vessel. It is seen at all ages, even in infancy,<sup>251</sup> more frequently among males. Treatment has been of little avail. The association with allergic conditions was discussed above in the section on allergy.

Grant<sup>252</sup> reports 7 cases in detail. He agrees with Leishman<sup>253</sup> that the rarity of the diagnosis must

be due at least in part to unfamiliarity with the disease. Many of the cases present a complex combination or succession of symptoms that sooner or later suggests the diagnosis. Grant lists his own experiences and gives a review of the majority of previously published cases, which number about 350. The pathology was well described in 1928 by Gruber,<sup>254</sup> and little has been added since. The various stages present in a single case agree with the clinical evidence that the lesions tend to occur in crops in the course of the disease, which may last for weeks, months or years. Since only short stretches of the affected vessels are attached, Grant emphasizes the necessity of examining excised tissue in serial sections. A characteristic of the disease is a changing clinical picture, fresh symptoms develop and older ones subside, often to recur, so that numerous diagnoses are made before the nature of the disease is recognized.

Leukocytosis may be extreme, with white-cell counts of 40,000 to 60,000. Rarely is there leukopenia. Eosinophilia is present in over 30 per cent of cases in which a differential count has been recorded, and the count may reach high figures—70 per cent in Strong's<sup>255</sup> case. The evidence suggests that periarteritis nodosa is much less rare than is generally believed, that it is not necessarily or even usually fatal and that it can be recognized at the bedside in a considerable proportion of cases.<sup>255</sup>

#### TREATMENT

Since the close of the recent war many remarkable advances in therapy have been announced. Streptomycin has been of definite value in tularemia and other serious diseases. O'Leary<sup>256</sup> states that although not the ideal agent for the treatment of cutaneous tuberculosis and tuberculids, it offers considerable promise because of its efficacy in guinea pigs inoculated with tuberculosis and because of the varying degrees of improvement in human beings. The therapeutic trials should be continued, and more should be done to stimulate laboratory investigations for a therapeutic agent that will have a more intense specific action against tubercle bacilli in human beings. New antibiotics, such as dihydrostreptomycin, a more stable derivative of streptomycin, and erythrin, extracted from the erythrocytes of rabbits, have been announced.

Radioactive isotopes and the nitrogen mustards have been introduced as agents of promise in therapy of diseases of the lymphoma group.<sup>257</sup> They are dangerous remedies, but in my opinion the relief—physical and symptomatic—of the cutaneous manifestations of these maladies outweighs the dangers of therapy. As yet evidence has not been obtained of any therapeutic effect by radioactive phosphorus (P32) on mycosis fungoides, xanthomatosis, melanoma, Ewing tumor, carcinoma of the breast or gall bladder or monocytic leukemia.<sup>258</sup> Radioactive phosphorus may be used externally for the treatment

of chronic lesions or growths.<sup>23</sup> Salutory results have been obtained with nitrogen mustard therapy in Hodgkin's disease, lymphosarcoma and chronic leukemia, with dramatic improvement observed in the first two disorders.<sup>24</sup>

Intravenous injections of ether have been used for pruritus and for relief of the painful ischemia in diabetes, Buerger's disease and Raynaud's disease. One may visualize many new possibilities, including less dangerous derivatives of nitrogen mustard gas and better control of radioactive phosphorus, in the treatment of nonfatal diseases such as atopic dermatitis.

Numerous authors have reported excellent results in the use of Benadryl and Pyribenzamine in various cutaneous eruptions, with stress on the results in urticaria.<sup>25-27</sup> I have tried them in almost every pruritic eruption seen in my office, from industrial dermatitis to dermatitis herpetiformis. About 20 per cent of the patients acquired some temporary relief, even those with the latter disease. With the exception of urticaria the pruritus recurred despite the fact that the patient continued to take the medication, in chronic urticaria relief stopped with cessation of the drug.

On the other hand new untoward effects are being added to those already known. Drowsiness, dizziness, weakness and nausea are the reactions most frequently encountered. Sixty-three per cent of patients in one series experienced side reactions, the chief one being drowsiness of varying degrees up to narcolepsy.<sup>28</sup> After taking 300 mg. of Benadryl for three days, 1 patient complained of palpitation, dimmed vision, malaise without drowsiness and heartburn with nausea. After the next regularly scheduled dose (making a total of 350 mg.) the patient was found unconscious in bed, cold, pale and pulseless. On the eleventh hospital day Benadryl was again started under careful observation. Again after 300 mg. for three days the patient had similar symptoms.<sup>29</sup> Borman<sup>30</sup> reports a case in which the patient became lethargic, confused and disoriented from an overdose of Benadryl, reported to be 2000 mg. in forty-eight hours. Slater and Francis<sup>31</sup> recently discussed the use of Benadryl as a contributing cause of an accident.

Granulocytopenia has been reported from the use of Pyribenzamine.<sup>32</sup> In 2 cases I have seen cutaneous eruptions following its administration. One was a papular eruption that disappeared with discontinuance of the drug and recurred with a test dose. The second occurred in a man who presented an extensive purpura with thrombotic ulcerations on the legs following the prolonged use of Pyribenzamine.

Para-aminobenzoic acid in combination with proper supportive therapy has relieved Rocky Mountain spotted fever. The results in 5 patients with this disease suggest that deaths from this

malady may be practically eliminated by such combined therapy.<sup>33</sup>

The pigmentation of adrenocortical deficiency has been arrested by grafts of adrenal glands, adrenocortical extracts and the synthetic desoxycorticosterone acetate.

Cutaneous eruptions have so many etiologic factors that no one remedy can be specific. Urticarial eruptions may be seen with almost any systemic disturbances, hence the varied medication, such as vitamin K.<sup>370</sup>

The use of vitamin A in skin diseases still commands attention. Much study has recently been devoted to the possible connection between certain cutaneous diseases and the levels of vitamin A in the blood plasma. Two British investigators<sup>371</sup> found little difference in the plasma vitamin A levels in 116 dermatologic patients and 116 control patients — a mean value of 116 international units of plasma in patients with skin disease and 113 international units in the controls. In 6 cases of Darier's disease, 2 of pityriasis rubra pilaris and 3 of ichthyosis, however, the mean level of vitamin A in the plasma was 77 international units. In the patients with Darier's disease and pityriasis rubra pilaris the administration of large doses of vitamin A concentrate resulted in an eventual plasma vitamin A level considerably above normal values. In 2 of the patients with Darier's disease the skin became normal or nearly so after treatment with vitamin A and Grenz rays. Two of the patients with pityriasis rubra pilaris showed some, but incomplete, improvement of the skin when the plasma vitamin A reached normal or higher than normal levels.<sup>372</sup>

Encouraging results have been obtained in ichthyosis by Gordon,<sup>373</sup> who postulates two types of therapy, the combination of which have brought him great success. Therapy consists of daily baths in 3 per cent sodium chloride solution followed by 10 per cent sodium chloride in hydrous wool fat and vitamin A internally in daily doses up to 200,000 units, with bile salts and neostigmine. Complete cure was effected in 1 case fifty-one days after treatment was started.

Charpy,<sup>374</sup> in France, and Dowling and Thomas,<sup>375</sup> in England, have reported extremely encouraging results with calciferol in the treatment of lupus vulgaris. Vitamin D<sub>3</sub> in propylene glycol was administered by mouth to a series of 39 patients, some of whom had old, stubborn and extensive lesions. Charpy considers a high calcium intake a necessary adjunct to calciferol therapy in this disease. The quantity of sodium chloride ingested was reduced. All 39 patients treated were completely cured, 12 of them by internal therapy alone.

At the last meeting of the Society for Investigative Dermatology Curris et al.<sup>376</sup> reported the successful use of calciferol and dihydrotachysterol therapy, with and without added calcium, in the treatment of sarcoid.



Norman<sup>277</sup> believes that vitamin D therapy, rather than parathyroidectomy, is the treatment of preference in scleroderma and the related disorders that are accompanied by hyperfunction of the parathyroid glands. He suggests that chronic overfunction of these glands constitutes a common denominator in scleroderma, dermatomyositis, chronic arthritis, Raynaud's disease and arteriosclerosis. He reports 3 cases of sclerosis, all with skin manifestations and apparently some muscle and tendon involvement. In all the cases improvement to the point of complete rehabilitation occurred, with restoration of normal skin and presumably a normal condition of the arterioles. Bernstein and Goldberger<sup>276, 279</sup> report the relief of scleroderma by dihydrotachysterol (AT-10). This substance, which is formed when tachysterol — one of the irradiation products of ergosterol — is treated with sodium and propyl alcohol, has a mild effect on increased excretion. In these effects it falls between vitamin D and parathyroid hormone. Dihydrotachysterol causes a marked increase in urinary phosphorus excretion as compared with vitamin D.

I have used AT-10 in 5 cases — 3 localized and 2 generalized. The results were somewhat encouraging in the localized but disappointing in the generalized cases. I have, however, had the same results with other medication. Careful laboratory studies of patients must be made during therapy with large doses of vitamin D. Kaufman et al<sup>280</sup> furnish fairly conclusive evidence that their patient died of high-potency vitamin D (ertron) intoxication.

Scleroderma is apparently associated with parathyroid dysfunction — either hyperfunction or hypofunction. Repeated serum calcium, total protein and phosphorus determinations should be done to determine the classification of the patient. If he falls in the hypoparathyroid group, dihydrotachysterol is the drug of choice. If he falls in the hyperparathyroid group, a partial parathyroidectomy should be performed, followed by large daily doses of vitamin D<sup>281-283</sup>. Cytochrome C may help. This substance, a protein normally present in all living tissue, may be injected to combat tissue anoxia. Proger and Dekaneas<sup>284</sup> believe that conditions in which anoxia is thought to play a role might be benefited by the injection of cytochrome C. Since there is considerable unused oxygen in venous blood, even in severe cases of anoxia, the role of cytochrome C is to promote utilization of the oxygen by tissues<sup>284</sup>.

Spies<sup>285, 286</sup> reported prompt regeneration of the blood and profound improvement in the glossitis following the administration of synthetic folic acid to 2 patients with macrocytic anemia in relapse and pellagrous glossitis.

New vitamins are constantly appearing. In 1939 Scarborough<sup>287</sup> presented evidence from experiments on human subjects to prove the existence of a factor decreasing capillary fragility, the factor being

vitamin P. Rutin, which like vitamin P is a flavone glucoside, is supposed to have the same properties. According to Griffith<sup>288</sup> it is a constituent of a variety of plants, including tobacco, garden rue, forsythia, elder flowers and violets. He administered rutin to 11 patients, capillary fragility became normal in 8 of these cases within two months after the beginning of medication.

Rutin therapy has been used in hereditary hemorrhagic telangiectasia<sup>289</sup>. Kushlan<sup>290</sup> gave a patient rutin in doses of 40 mg three times daily. A remarkable change in the character of the bleeding was noted twenty-four hours after the start of medication. The daily epistaxis and bleeding from the gums ceased for the first time since childhood and had not recurred at the time of writing.

A recent editorial seems somewhat timely. It reads as follows:

Rutin is a new agent for which certain therapeutic claims have been made with reference to disturbances of capillary fragility and permeability. Rutin is said to be a glucoside of quercetin, which can be obtained from various leafy plants and flowers. Just how it is supposed to act is not clear. When we recall that capillary permeability and so-called "fragility" may be altered either by disorders of the capillary membrane itself or on the other hand by changes in the cement substance between the endothelial cells, and when we realize that the cement substance in turn is affected by all sorts of variations in reaction and in concentration of various blood ions, it becomes clear how complicated the situation is and how difficult a really critical evaluation of any substance from the standpoint of its effect on "capillary fragility" must be. To call rutin vitamin "P" or give it such a general designation as the capillary permeability regulating vitamin hardly seems justifiable as yet. It has been found, however, that the use of rutin may be followed by lessening of capillary permeability under certain conditions as measured by a standard petechiometer test. Since the material seems to produce no toxic effects in man and furnished in the form of a small, practically tasteless pellet which can be taken simply by mouth, a thorough appraisal in clinical conditions in which capillary fragility is altered seems worth while.<sup>291</sup>

Perhaps rutin is not harmless. Two cases of subconjunctival hemorrhages are reported — the first after approximately four and eight weeks of rutin therapy, and the second after one day's administration of this drug<sup>292</sup>.

The scope of penicillin is constantly enlarging. It has been used in the treatment of patients with various cutaneous infections<sup>293-296</sup>. Zee<sup>297</sup> reports a case of relapsing febrile nonsuppurative panniculitis (Weber-Christian disease) observed in a twenty-three-year-old soldier, the lesions being proved by biopsy. Treatment with sulfadiazine was unsuccessful. The findings and symptoms were progressive until the institution of treatment with penicillin. Doses of 20,000 units each were given intramuscularly for a period of fifteen days, to a total of 2,360,000 units. Within three days after the institution of treatment the temperature returned to normal and remained there. No further lesions were noted. The nodules regressed, and during a period of three and a half months there was no recurrence of symptoms or findings.

Physicians treating arthritis with gold are now observing the reactions described years ago by dermatologists who first used this metal in the treatment of discoid lupus erythematosus. For combating these reactions they are fortunate to be able to obtain BAL. This substance, whose chemical name is 2,3-dimercaptopropanol, was developed by the British as an antidote to arsenical blister gases.<sup>199</sup> But long before World War II — indeed during the era of Paul Ehrlich — studies leading to the recognition of the clinical value of BAL were being made.<sup>200</sup> Two serious reactions to gold salt — thrombopenic purpura and granulocytopenia — are described in an article by Lockie et al.<sup>201</sup> Spectacular recovery occurred in each case. The usual course of such complications appears to have been definitely altered by BAL therapy. No change in the status of the arthritis occurred. Ragan and Boots<sup>202</sup> used this drug successfully in 5 patients with dermatitis due to gold. Successful treatment with intramuscular injections of BAL was also reported by Cohen and his associates<sup>203</sup> in 5 cases of acute poisoning due to gold and 1 of acute poisoning due to arsenic. Transient symptoms of BAL toxicity included a sense of warmth in the mouth, salivation, flushing of the face, conjunctival injection, lacrimation and pains in the arms and legs. The number of cases reported is too small to justify a definitely favorable interpretation of results, and yet the prompt clinical effects are impressive and warrant more extended use of this drug in the relief of gold intoxication, so that eventually chrysotherapy of rheumatoid arthritis may be employed more generally and with less fear of the devastating toxic reactions.<sup>204</sup>

Hartman<sup>103</sup> acclaim the use of hormones in dermatology, citing the diseases due to their deficiency or absence of a specific endocrine product responding to substitutive therapy, disorders not due to a specific hormone deficiency, but in which a hormone has a specifically useful effect, and those in which endocrine malfunction may be a precipitating or aggravating factor.

In the first group he mentions adrenocortical extracts and synthetic desoxycorticosterone acetate in Addison's disease, desiccated thyroid or thyroxin in myxedema, pituitary or chorionic gonadotropin in urticaria and dermatographia, estrogens in pruritus vulva and senile vaginitis, and the value of insulin in xanthoma diabetorum and other skin manifestations of diabetes mellitus.

The second group includes epinephrine, pitressin and insulin in urticaria and angioneurotic edema, parathyroid in papular urticaria, pitressin in herpes zoster and desiccated thyroid in xanthoma tuberosum, xeroderma, ichthyosis and seborrheic dermatitis. Estrogens are suggested for therapy in Cushing's syndrome, gonorrheal vulvovaginitis before puberty and vulvovaginitis due to Trichomonas during and after the menopause.

In the third classification there is an interesting discussion of the relation of thyroid or gonadal malfunction in atopic dermatitis, urticaria and acne vulgaris. Hartman<sup>205</sup> states that in the present state of knowledge no good can be done to the acne or atopic dermatitis in male patients and that conceivable harm can be done to the pituitary-gonadal equipment. In the female one gets the impression there are menstrual and premenstrual types, but the persistence of the lesions makes distinction difficult.

I might suggest a word of caution to gynecologists and dermatologists. Three indignant women have sought my advice regarding the increased growth of hair on the face subsequent to the injection of testosterone.

### CONCLUSIONS

After reading the foregoing discussion, the physician should realize that any cutaneous disturbance that resists simple medication warrants thorough study of the patient. Even a simple wheal may be the beginning of a serious illness, likewise, the sudden onset of a cutaneous eruption in an extremely sick patient may prognosticate a fatal ending. Having remarked on the necessity for the increased use of powers of observation and palpation among physicians, I might decry the extreme to which these powers are used by some dermatologists, who frequently rely too much on observation of cutaneous lesions and neglect complete physical examination and necessary laboratory procedures.

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assumption of previous hypertension, and in this terminal period the blood pressure was low.

Could the patient have had multiple pulmonary infarcts resulting in cardiac failure of the cor-pulmonale type? There is no note of an accentuation of the pulmonary second sound. It is true that the systolic murmur may have been pulmonary in origin, but we should have more evidence of right-sided heart strain as the primary difficulty. There were no acute episodes in the past suggesting pulmonary infarction. As for the unexplained primary myocardial lesion, the unusual types of true myocarditis that we have seen in these sessions, such as those related to the sulfonamides or isolated or diffuse myocarditis, such cases are usually seen in younger patients, certainly, in the type associated with virus infection, there is very often a story of pre-existing respiratory infection. There is no reason to believe that there was an aortic aneurysm, whether on an atherosclerotic or on a syphilitic basis. We have, however, no x-ray studies on this patient.

To return to the evidence as it is given to us we should think of calcific aortic stenosis. The points that go with that diagnosis are the male sex, the fact that cardiac failure often appears late in life, the large left ventricle, congestive failure with normal rhythm and the rather rapid downhill course. I am disturbed particularly by the electrocardiographic findings in that there was no left-axis deviation, which one would expect in prolonged disease of the aortic valve. However, yesterday in the clinic we saw a man who had had a known aortic lesion of rheumatic origin for thirty years in which there was little if any left-axis deviation. To get around that difficulty one might mention the possibility of a complicating mitral lesion with a balanced electrical effect on the electrocardiogram, of which we have no clinical evidence, or we might introduce the Bernheim syndrome, which is a bulge of the septum into the right ventricle in lesions that produce marked enlargement of the left ventricle. However, one would expect such a condition to interfere with filling of the right ventricle, and that has been brought forth as an explanation for the signs of primary right-sided heart failure in systemic hypertension.

I know that we have frequently been found wanting in our ability to diagnose calcific aortic stenosis in elderly patients who are in extremis, or who are admitted to the hospital for surgical operation, and who never knew they had anything wrong with the heart. One can infer that a businessman may have had physical examinations throughout his lifetime or even tried to take out life insurance and may have known something about heart disease in the past, but the record contains no such statement. The fact that he was given nitrates previously suggests that before admission he had a doctor, who might tell us about the physical findings. But I confess that I shall have to say that this diagnosis

of aortic stenosis appeals to me most. There may have been in the background a congenital bicuspid aortic valve, or some stigmas of a previous rheumatic infection. The final episode, which was associated with pulmonary edema and deep cyanosis, suggests a terminal pulmonary infarction. Statistically I should judge that that would be found. On the other hand patients with aortic stenosis, with characteristic encroachment on the coronary ostia, may die suddenly, and in this case the cyanosis could well have been due to the extreme degree of moisture in the lungs without pulmonary infarction.

Dr. TRACY B. MALLORY: Dr. Chapman, would you like to comment?

Dr. EARLE M. CHAPMAN: I arrived too late to hear all the discussion but at this point I want to congratulate Dr. Sprague on his astute diagnosis. I am the physician who saw the patient and followed him for some three years. He came to me primarily as a patient with mild diabetes and merely for control of the diabetes. His health had been otherwise good, he had no primary complaint and claimed that he was well, and I thought him to be so. Examination disclosed the harsh systolic murmur, loudest along the left border of the sternum and apex. I thought that it was somewhat transmitted in the aortic area, and yet I did not interpret it at the time as a murmur of aortic stenosis. I thought, rather, that perhaps in youth he had had rheumatic infection and might have mitral insufficiency to a mild degree. He developed a papilloma or carcinoma of the bladder in the summer of 1946, which was treated by fulguration. He withstood the procedure very well, came home and resumed his usual activity. At all times the rhythm was regular, and the rate slow. There was no indication of heart failure until the spring of 1947, when he began to complain of some shortness of breath. He knew that he was aging, — he was by that time sixty-eight years old — and in climbing the subway stairs was short of breath when he reached the top. At other times he had a feeling of pressure under the sternum — not pain, but simply pressure. This was interpreted by me as being mild angina, and I gave him 0.1 gm. of Aminophylline three times a day. He was not given nitroglycerin. In August, while attempting to transport his wife, who is an invalid, in a sedan chair, with the aid of another friend, he suddenly had a violent attack of shortness of breath. About two weeks later I visited him at his home. At that time he was in the garden, and we had to walk across the entire garden and up to the bowling green and then up another 20 feet to the house and up two flights of stairs. I observed no undue dyspnea or complaint on his part, although I was definitely short of breath. At that time he did not seem to have any signs of congestive failure, and I saw no reason to give digitalis. But I arranged for a consultation with a

member of the Cardiac Department That was on September 8 You have heard the rest of the history He died on September 20 I did not see him in the last illness, which terminated in the course of twenty-four hours

A PHYSICIAN Did he have an aortic thrill?

DR CHAPMAN No, there was no thrill

DR SPRAGUE Some years ago, when we collected a series of cases of "pure" mitral regurgitation and "pure" mitral stenosis, in the group of twenty patients with "pure" mitral regurgitation the systolic murmur was loudest at the apex<sup>2</sup> We followed these 20 cases for several years, and 2 of the 20 patients with what we thought was originally mitral regurgitation turned out later to have aortic stenosis and the murmur became more intense at the aortic area

#### CLINICAL DIAGNOSES

Acute pulmonary edema  
Coronary thrombosis with myocardial infarction?  
Coronary heart disease  
Angina pectoris

#### DR SPRAGUE'S DIAGNOSIS

Calcific aortic stenosis

#### ANATOMICAL DIAGNOSES

*Calcific aortic stenosis*  
Acute pulmonary edema, severe  
Arteriosclerosis

#### PATHOLOGICAL DISCUSSION

DR MALLORY Autopsy showed a considerably hypertrophied heart, which weighed 595 gm, with calcareous aortic stenosis and no other valvular lesions The cusps of the aortic valve were not interadherent but were markedly calcified, and it was impossible to thrust even the tip of the finger between the calcified masses The coronary arteries were sclerotic and calcified in part but showed no areas of significant narrowing and no evidence of old thrombosis The myocardium was free from scars grossly and microscopically, so that all our evidence is that of a pure aortic stenosis The lungs of course were extremely heavy, weighing over 2400 gm — as marked a pulmonary edema as one ever sees There were no other significant findings and no evidence of recurrence of the tumor The degree of passive congestion in the liver, spleen and kidneys was very slight

DR SPRAGUE Was there pulmonary infarction?

DR MALLORY No

DR SPRAGUE Had he had x-ray studies prior to the ones of the heart? Was he a thick individual or thin?

DR CHAPMAN He was a thin man He had an increased anteroposterior diameter of the chest, a barrel-shaped chest, although he had small arms and legs

DR SPRAGUE The most useful thing in diagnosis of this sort, of course, is careful fluoroscopic examination If the examiner takes a long enough time to get his eyes accommodated he can usually see calcifications in the aortic valves in an elderly person with aortic stenosis and observe the characteristic rotary motion of the valve

DR CHAPMAN He had fluoroscopic studies, and that was not observed

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#### CASE 33512

#### PRESENTATION OF CASE

A fifty-eight-year-old shoe-store operator entered the hospital because of a lump in the neck

The mass suddenly appeared nine weeks before entry while the patient was taking a bath It was in the anterior portion of the neck occupying most of the space between the chin and sternum, and was painless, although for several days it was tender, with redness of the overlying skin The mass had diminished slightly in size There had been no other symptoms, and the patient felt quite well Two determinations of the basal metabolic rate taken soon after the lump appeared were reported as normal

The patient had had diabetes for three years and took 18 units and 36 units of regular insulin on alternating days The urine remained sugar-free most of the time He had been treated for syphilis twenty-eight years before entry, and several blood tests since then had been negative

Physical examination revealed a firm, rubbery, rounded mass, measuring 8 by 7 by 4 cm, projecting from the thyroid area, rather more so on the right It was slightly warm and nontender, and no bruit or pulsation was present The mass was fixed but moved vertically with swallowing Two small, firm lymph nodes were present at the lower end of the left side of the mass at the base of the sternocleidomastoid muscle A harsh Grade II systolic murmur was audible at the apex and base of the heart There were small bilateral inguinal hernias

The temperature was 97.8°F, and the pulse 80 The blood pressure was 180 systolic, 108 diastolic

Examination of the blood disclosed a red-cell count of 4,980,000, with a hemoglobin of 13.5 gm, and a white-cell count of 7700, with 66 per cent neutrophils The urine had a specific gravity of 1.022 and gave a ++ test for albumin and an orange test for sugar The sediment contained an occasional red cell and pus cell The fasting blood sugar was 173 mg, and the nonprotein nitrogen 31 mg per 100 cc The stools were guaiac negative

X-ray examination showed a mass in the upper anterior portion of the mediastinum measuring 8 cm across and extending down beneath the manubrium sterni. The esophagus was deviated slightly to the left but was not compressed. In the right lower-lung field was an area of increased density superimposed over the ninth rib posteriorly and the fifth rib anteriorly. This was not seen in a lateral view.

The patient was given no specific therapy. On the fourth hospital day 500 microcuries of radioactive iodine was given, and surface counts showed less activity over the tumor. On the fifth hospital day an operation was performed.

### DIFFERENTIAL DIAGNOSIS

DR EDWARD HAMLIN, JR. The first intriguing remark in the protocol is that the mass suddenly appeared while the patient was taking a bath. If we accept that as a valid observation, we would immediately come to a full stop, for there is no condition of which I am aware in which a mass of this size can suddenly appear while a patient is taking a bath. Therefore, we must assume that the patient first noticed it then, but that it had been gradually appearing over an indefinite period.

For the moment I shall dispense with the diabetes and assume that it had no relation to the disease.

From the physical examination, one can only conclude that this mass was in some way related to the thyroid gland, since it moved on swallowing. Assuming that this is so, there are three entities that must be considered in the differential diagnosis: cancer, inflammation and a cyst or involutional type of goiter. The fact that the mass was fixed makes it appear unlikely that a simple colloid or involutional goiter was responsible. It is frequently impossible to differentiate chronic thyroiditis and cancer of the thyroid gland. The two small firm lymph nodes, which were found at the lower end of the left side of the mass at the base of the sternocleidomastoid muscle, could be attributed to either disease. The mass seen in the right lower-lung field, only in the anteroposterior view, if we think in terms of one diagnosis could be associated only with cancer.

Nothing else in the protocol seems to be at all helpful in the differentiation of these two conditions. It would be nice to have had a report on whether the vocal cords moved equally.

DR BENJAMIN CASTLEMAN. I note in the record that the larynx was examined by a member of the Eye and Ear Infirmary and that the vocal cords were found to be normal.

DR HAMLIN. Cancer of the thyroid gland frequently invades the region of the recurrent laryngeal nerve or nerves and produces a paralysis, which is almost unheard of in any other condition of the thyroid gland.

Probably the only sure way to make an accurate diagnosis was the method employed, which was operation with a biopsy—a frozen section of the tissue itself—and only then could the proper treatment be carried out.

One obscure sentence in the protocol is that radioactive iodine was given and surface counts showed less activity over the tumor. Less activity than what? In either thyroiditis or carcinoma the amount of iodine that would be absorbed might be very low indeed, and the activity would certainly be less than that over a normal thyroid gland.

On the whole, with a questionable lesion of the lung, I should be inclined to call this carcinoma of the thyroid. Certainly, in several cases that we have recently seen, such a carcinoma was an extremely rapidly growing and very malignant tumor, which I suspect that this proved to be. Therefore, carcinoma of the thyroid gland is my first choice, and the second is chronic thyroiditis.

DR WILLIAM M. JEFFERIES. When this patient was seen at the Thyroid Clinic there was considerable speculation concerning the diagnosis of the mass in the neck. On palpation this was thought to feel more like carcinoma, but the history of sudden appearance could not be shaken. The patient maintained that the mass had not been present prior to the day he first noticed it since he previously had not seen or felt any unusual swelling in the course of daily shaves, nor had he experienced difficulty in buttoning his collar. His wife corroborated this statement. The associated signs of inflammation, notably tenderness, heat and redness, were also unusual for carcinoma of the thyroid gland, although it could conceivably have resulted from sudden hemorrhage into a rapidly growing tumor.

For these reasons other possibilities were considered. Sudden hemorrhage into a cyst of the thyroid gland might account for the acute enlargement with associated inflammatory signs, but the neighboring lymphadenopathy would be unexplained. Acute thyroiditis might produce such a picture, but with a swelling of this size one would expect to find associated constitutional signs such as fever and leukocytosis. With the history of syphilis in the past, gumma of the thyroid gland was mentioned, but this is such an extremely rare condition (and the patient had apparently had adequate treatment) that it was thought to be unlikely. It was therefore believed by the majority of examiners that this was most probably a malignant tumor.

The studies with the Geiger counter after the administration of a tracer dose of radioactive iodine revealed less radioactivity over the main portion of the mass than over its posterolateral edges, suggesting that the functioning thyroid tissue had been displaced posteriorly by the mass.



## CLINICAL DIAGNOSIS

Carcinoma of thyroid gland?

## DR. HAMLIN'S DIAGNOSIS

Carcinoma of thyroid gland

## ANATOMICAL DIAGNOSIS

*Carcinoma of thyroid gland, giant-cell type*

## PATHOLOGICAL DISCUSSION

DR. CASTLEMAN At operation a firm somewhat fluctuant mass adherent to the strap muscles was disclosed. Aspiration produced a cloudy sero-sanguineous material containing small fragments of tissue, which on frozen section seemed to be necrotic, with a predominance of polymorphonuclear cells. A biopsy of the thick wall of the mass revealed a very undifferentiated carcinoma, and a total thyroidectomy was performed.

We received about 120 gm of tissue containing nodules of necrotic tumor, some normal thyroid tissue and several lymph nodes that proved to be uninvolved, but the tumor had invaded some of the adjacent strap muscles. The semifluctuant area originally observed and aspirated was a focus of necrosis and hemorrhage and probably accounted, in part at least, for the sudden appearance of the mass.

Microscopically this tumor fits into the more malignant group of thyroid tumors, in which the cells are very large and undifferentiated, some being spindle-shaped and others multinucleated tumor giant cells. Because one portion is sometimes composed predominantly of spindle-shaped cells, the tumor has often been called a sarcoma or carcinosarcoma. However, most pathologists now believe that this type of tumor is fundamentally epithelial and prefer the term "giant-cell carcinoma."

Postoperatively the patient received a total of 5700r to the anterior portion of the neck and mediastinum over a period of one month.

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## THE WISE MEN

Among the many inspiring stories associated with Christmas is the familiar one of the wise men who came from the east to Bethlehem. They were only three in number, they were guided through the darkness of the desert by the light of a star, and when they had found that which they sought they left gifts and departed into their own country by another way, fearing Herod.

The proportion of wise men to foolish in the world today is generally the same as it was when Christianity dawned, and we still have our Herods. Men and women continue to be of about the same material that their inheritance has determined, polished or marred by that with which it comes in contact. They are still ignorant, passionate, selfish, unsophisticated, cruel and kind grasping and

They have, however, something that the world once lacked — the same star to guide them that the wise men followed.

No one who has been exposed to the great religious forces of the world can escape being influenced in some positive way by them. Names and forms matter little. Each has its divine leadership, each has its Herods, each its crosses, its stars or its crescents, each has its wise men and each its growing tolerance.

It is on this that the salvation of the future will depend. It is on the mutual respect and forbearance and understanding that must be building between races and colors and creeds each for the others.

## SHORTENED ISOLATION REQUIREMENTS

THE advance of knowledge regarding the common communicable diseases has resulted in the shortening of many isolation requirements. A case of meningococcal meningitis, under prompt and adequate sulfonamide treatment, can be considered no longer infectious after five days, and the same thing may be said of the quarantine of treated contacts. Recent clinical investigations have shown that the virus of chicken pox is apparently spread from the respiratory tract for two to four days prior to the eruption, and that the period of infectivity does not appear to extend beyond the fifth day after the appearance of the skin lesions.<sup>1</sup> According to these observations, prolonging the isolation beyond one week, until the scabs fall off, seems to be unnecessary. On the other hand, the old idea that smallpox is contagious for the duration of the crusts is borne out by recent observations.<sup>2</sup> The virus of mumps has never been isolated from the saliva beyond seventy-two hours of the onset of the parotitis, yet no experimental evidence is at hand to determine whether other late manifestations of this disease imply a renewed secretion of the virus through the salivary glands. Therefore, precautions should be continued until this point has been determined.

The infectivity of measles begins during the prodromal catarrhal stage and extends through the height of the eruption, falling off promptly as the rash fades. Again, in whooping cough, it has been found that 71 per cent of cases originate from ex-

posure to patients in the prodromal catarrhal stage, 18 per cent from exposure in the first week of the paroxysmal stage, 8 per cent in the second week, and 2 per cent in the third week.<sup>3</sup> This curve conforms fairly closely to that of positive cultures obtained with cough plates.<sup>4</sup> In this disease, however, the duration of infectivity, although diminishing materially, warrants isolation for a period of at least three weeks, and even longer for the protection of infants in the first months of life. The problem of isolation for rubella is especially concerned with the protection of women in the early months of pregnancy. Here, as in these other diseases, it is to be emphasized that the period of infectivity begins prior to the stage in which the disease can be recognized by the classic symptoms and that isolation is usually applied too late to be more than partially effective.

Poliomyelitis and scarlet fever present extraordinary problems of isolation because both diseases are peculiar manifestations of widely disseminated infections that, in minor forms, go unrecognized except by cultural methods. New or renewed concepts arrived at through laboratory experiments are often in conflict with observations based on careful field studies in epidemiology, which point to their predominantly air-borne and person-to-person dissemination. Nevertheless, a shortening of the isolation requirements of both these diseases is in progress owing to the results of these studies.

State boards of health are usually better informed in such matters than local boards of health. The former establish minimum requirements of isolation and quarantine, whereas the latter are free to impose stricter measures. If a local board desires to try out a time limit below the minimum established by state or federal standards the right to do so should be granted. Indeed, permission to do so should be granted to qualified medical directors of educational institutions by local and state authorities. In support of this contention one can point to the classic method of curtailing scarlet fever isolation in the city of Bergen, Norway, twenty-five years ago,<sup>5</sup> recently adopted with modification in parts of the United States, and to the satisfactory results of shortened isolation procedures in other common communicable diseases at Rugby School in England.<sup>6</sup>

The health authorities of New England have always been ready to co-operate in any well planned studies related to the economic factors of disease control.

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## MASSACHUSETTS MEDICAL SOCIETY

### DEATHS

COYNE — Thomas J. Coyne, M.D., of Roxbury, died on December 4. He was in his seventy-fifth year.

Dr. Coyne received his degree from Tufts College Medical School in 1901. He was a member of the staffs of St. Elizabeth's, St. Margaret's and Harley hospitals. He was a fellow of the American Medical Association.

Two sisters and a brother survive.

MENARD — Leon J. Menard, M.D., of Fall River, died on August 9. He was in his fifty-sixth year.

Dr. Menard received his degree from University of Vermont College of Medicine in 1919. He was formerly a member of the Fall River Board of Health and was a member of the staff of St. Anne's Hospital.

His widow, three sons, two brothers, three sisters and one grandchild survive.

STONE — Jane Gray Stone, M.D., of Boston, died on May 6. She was in her seventy-fourth year.

Dr. Stone received her degree from Tufts College Medical School in 1911. She was a former member of the Massachusetts Medical Society.

Three brothers and a sister survive.

## MISCELLANY

### NOTES

The following appointments to the teaching staff of Harvard Medical School were recently announced: Marvin Morton Nachlas, of Boston (A.B. Johns Hopkins University 1940, M.D. Johns Hopkins University 1943), assistant in anatomy; George William Lynch, of Boston (A.B. Harvard University 1929, M.D. Harvard University 1933), assistant in medicine; Peter Bernard Golden, of Boston (S.B. University of Wisconsin 1938, M.D. University of Wisconsin 1940), assistant in surgery; Thomas Simpson Risley, of Waterville, Maine (S.B. Harvard University 1937, M.D. Harvard University 1941), assistant in surgery; Stanton Lee Eversole, Jr., of Charlottesville, Virginia (M.D. University of Virginia 1944), teaching fellow in physiology; Sidney Cobb, of Fort Devens (S.B. Harvard University 1938, M.D. Harvard University 1942), research fellow in biologic chemistry; Harold Mankin, of Teaneck, New Jersey (A.B. Columbia University 1938, M.D. Harvard University 1942), research fellow in biologic chemistry; Robert Buka, Jr., of New York City (A.B. Harvard University 1938, M.D. University of Pittsburgh Medical School 1942), research fellow in medicine; Pedro Maximino Catoggio, of Republica Argentina (M.D. Universidad Nacional de La Plata 1943), research fellow in medicine; Harvey Shields Collins, of Boston (S.B. University of California 1935, A.M. Harvard University 1940, M.D. Harvard University 1943), research fellow in medicine; David Thomas Dresdale, of

Brooklyn New York (M.D. College of Physicians and Surgeons Columbia University 1942) research fellow in medicine Paul Fremont-Smith of Cambridge (M.D. Harvard University 1946), research fellow in medicine Edward Phillips of Los Angeles, California (M.D. University of Southern California 1942), research fellow in medicine David Harris Solomon, of Brookline (A.B. Brown University 1944 M.D. Harvard University 1946) research fellow in medicine Edward Donnell Thomas of Boston (A.B. University of Texas 1941 A.M. University of Texas 1943 M.D. Harvard University 1946) research fellow in medicine Niilo Oskar Birger Hallman of Helsinki Finland (M.D. Medical School of University of Helsinki, Finland 1943) research fellow in pediatrics, Daniel Charles Tosteson, of Wauwatosa Wisconsin (no degree) research fellow in physiology Eugene Leonard Watkins of Worcester (A.B. Clark University 1940 M.D. Harvard University 1943) research fellow in surgery Lawrence Chappell Kingsland Jr. of Wakefield (S.B. Mass Institute of Technology, M.D. Harvard University 1940) instructor in pediatrics John Schulman, Jr., of New York City (S.B. Yale University 1942 M.D. University of Pennsylvania 1946), research fellow in medicine William A. Messner, of Newton Center (A.B. University of Oregon 1935 M.D. University of Oregon Medical School 1938) instructor in pathology, William Fields Cavensue of Raleigh North Carolina (A.B. University of North Carolina 1929, M.D. McGill University Medical School 1943) assistant in psychiatry Janice Hodges, of Metairie, Louisiana (S.B. Louisiana State University 1942, M.D. Louisiana State University Medical School 1944), assistant in psychiatry David John Myerson, of Brookline (A.B. Harvard University 1940, M.D. Tufts College Medical School 1943) assistant in psychiatry, Jackson Smith, of Normal, Oklahoma (A.B. University of Oklahoma 1939 M.D. University of Oklahoma 1943) assistant in psychiatry, Fadil Adjady, of Mosul Iraq (M.D. Faculty of Medicine of Paris 1937), research fellow in bacteriology and immunology, Nusret Hasan Fisek, of Ankara, Turkey (M.D. Medical School of University of Istanbul 1938), research fellow in bacteriology and immunology, Ching teng Teng, of Chungking Szechuan Province China (S.B. Yenching University 1935 M.D. Peiping Union Medical College 1941), research fellow in biologic chemistry Norman Robert Stanley Hollier, of Ottawa Ontario (B.Sc. University of Alberta 1944 Ph.D. McGill University 1947) research fellow in physical chemistry Rudolf Georg Straasale of Berne Switzerland (Ph.D. University of Berne 1946), research fellow in physical chemistry Robert Peter Brittain, of Scotland (B.Sc. 1939 B.L. 1941 M.A. 1943, M.B., Ch.B. 1943, LL.B. 1944; D.P.A. 1943—Glasgow University), research fellow in legal medicine Arnold Michael Cooper of Roselle New Jersey (A.B. Columbia College 1943, M.D. University of Utah Medical School 1947) research fellow in medicine; Lillian Recant, of New York City (A.B. Hunter College, 1941 M.D. Columbia University 1946), research fellow in medicine, and Robert Warren Reifenstein, of Syracuse, New York (A.B. Syracuse University 1943 M.D. Syracuse University 1945), research fellow in medicine.

#### ROCHE-ORGANON AWARDS IN ENDOCRINOLOGY

Three awards of \$500 each have been sponsored by Roche-Organon Inc. hormone manufacturers, for scientists in recognition of their recent, outstanding research in the following fields of endocrinology: animal experimentation hormone chemistry and clinical endocrinology. The winners of the 1947 awards are Dr. Fuller Albright (clinical endocrinology) Dr. Robert D. H. Heard (hormone chemistry) and Dr. Dwight J. Ingle (animal experimentation). The winners of the awards were selected by the Committee on Awards of the Laurentian Hormone Conference which consists of Dr. Roy G. Hoskins chairman and Drs. Edwin B. Astwood Thomas F. Gallagher Allan T. Kenyon Robert L. Noble and Abraham White. The awards were presented at the 1947 Laurentian Hormone Conference held recently at Sainte Adèle, Quebec, Canada.

#### MASSACHUSETTS CENTRAL HEALTH COUNCIL

Appointment of a nutrition committee, consisting of the following members, was recently announced by the Massachusetts Central Health Council Frederick J. Stare, M.D.

(chairman) professor of nutrition and head Department of Nutrition Harvard Medical School associate in medicine, Peter Bent Brigham Hospital member Food and Nutrition Board National Research Council and formerly consultant in nutrition to the Surgeon General United States Army, Charles C. Lund M.D. assistant professor of surgery Harvard Medical School, and visiting surgeon Boston City Hospital George Thorn M.D. professor of medicine Harvard Medical School and physician-in-chief Peter Bent Brigham Hospital Charles S. Davidson M.D. instructor in medicine Harvard Medical School assistant physician, Thorndike Memorial Laboratory, and assistant director, Fourth Medical Service Boston City Hospital, and formerly consultant in nutrition to the Surgeon General, United States Army Robert Harris, Ph.D. professor of nutritional biochemistry Massachusetts Institute of Technology and consultant in nutrition to the Pan American Society and to the Quartermaster General United States Army, Elda Robb Ph.D. professor of home economics and head department of Home Economics Simmons College Mrs. Beulah Becker Marble formerly president American Dietetic Association Mrs. Emma May acting head Nutrition Board Massachusetts State Department of Health Miss May Foley extension nutritionist, Massachusetts State College, Amherst and Miss Jean Ackerman supervisor of nutrition Boston Visiting Nurse Association.

#### WORLD HEALTH ORGANIZATION

The World Health Organization of the United Nations demonstrated its effectiveness in the epidemic of cholera in Egypt this fall. An important part of the demonstration was the co-operation of various nations against a common danger.

More than 32 tons of vaccine, plasma and other supplies were shipped from New York by air. China made available 2,000,000 cc. of vaccine and Indo-China, Japan and Southern Korea more than 3,200,000 cc.

This is the first time in history according to the report released on December 1 that an epidemic spreading at a rate of more than a thousand new cases a day has been checked within six weeks of its onset. Final figures indicate that 20,129 cases occurred with 9,760 deaths. The case fatality rate was about 48.5 per cent, as compared with former rates in the vicinity of 85 per cent.

#### FELLOWSHIPS FOR RESEARCH IN OPHTHALMOLOGY

Dr. Thomas Duane of Harvard Medical School, and Dr. David Freeman of Yale University School of Medicine have been awarded fellowships for research in ophthalmology by the Eye Bank for Sight Restoration Inc. Dr. Duane will investigate the metabolism of the cornea under various conditions of storage to determine the factors that affect corneal tissue and make it unsuitable for corneal transplant, and Dr. Freeman will conduct an experiment in tissue transplantation to determine whether embryonic tissues can be grafted upon members of the same or different species. It is hoped that the knowledge acquired through these investigations will aid in the conservation of vision and the restoration of sight among thousands of persons.

#### CORRESPONDENCE

##### DIAGNOSIS FIRST

To the Editor: Many years ago Dupuytren told his students "Diagnosis holds the first rank in our science and is the most difficult part of it without an exact and precise diagnosis theory is always faulty and practice often incorrect."

After reading the article "Clinical Significance of Malignant Neoplasms of the Thyroid Gland" by Rogers et al. in the October 16 issue of the *Journal* I am convinced more than ever of the wisdom and soundness of Dupuytren's teaching. If it is the chief duty of an attending physician to make a precise diagnosis and when a patient

is attended who has a nodule in the thyroid gland, I know of no way of making such a diagnosis without excising the diseased area and submitting it to a microscopist competent in the diagnosis of tissues

MALCOLM THOMPSON, M D

1711 Heyburn Building  
Louisville, Kentucky

Dr Thompson's letter was referred to Dr Walter F Rogers, Jr, whose reply is as follows

*To the Editor* It would be difficult and unwise to question the wisdom of Dupuytren's maxim, which was quoted in Dr Thompson's letter, and it was not the purpose of our paper to create the impression that an exact and precise diagnosis is not desirable. On the other hand, the purpose was to discuss the incidence, course and importance of malignant neoplasms of the thyroid gland. This included such facets of the problem as the significant number of complications associated with operations on nontoxic goiters and recurrence or development of malignant lesions despite "prophylactic surgery."

Dr Thompson's letter indicates his belief that if a patient has a nodule in the thyroid gland it should be removed. We also concluded that most solitary nodules should be extirpated and examined microscopically by a pathologist, thus, it seems that here we are in essential agreement. It may be added that the diagnosis of a malignant neoplasm of the thyroid gland, even by histologic examination, is not always unequivocal or easy, for many pathologists admit the great difficulty of determining whether some thyroid nodules are or are not the site of malignant growth.

After data have been accumulated, it is not surprising that their interpretation may differ. However, when all aspects of the problem of malignant neoplasms of the thyroid gland are considered, our judgment of the evidence leads us to believe that it is wise to remove single nodules, but that the routine surgical extirpation of all nodular goiters is not necessary or advisable.

WALTER F ROGERS, JR, M D

Thorndike Memorial Laboratory  
Boston City Hospital

## CONTRACEPTIVE CARE A REBUTTAL

*To the Editor* Is it a blot on the legislative escutcheon of Massachusetts to have overridden the previously proposed Sangerism? Are we wet blankets or wallflowers in a materialistic and pseudoscientific era to oppose such an enactment? I say pseudoscientific advisedly, any means which seems to justify an academic whim seems to be correct protocol. Is this the scientific method?

This pending bill is a further attempt to legalize the practice of birth control and as such has no place on our legislative referenda. Notwithstanding the pre-eminent roll call of co-sponsors it is my desire to discuss the amendment. The idea of giving contraceptive advice to married women is hardly commensurate with the practice of ethical medicine.

Ethics is nothing more or less than the science of morality. Morality is the norm which delineates between right and wrong. These norms were not established by us nor can they be transcended by us. This situation obtains in every field of endeavor, and by the same token it must be incumbent on every physician so to govern himself.

Is the giving of contraceptive advice right? Does it adhere to the moral law or is it a relative issue? I say, "No," because it is irrevocably alien to the primary ends of marriage. It is an unnatural and artificial frustration of a faculty given to us in marriage.

I am keenly aware of the many conditions precluding childbirth. Do these necessitate the use of means which are essentially wrong? Is not self-control the answer or does it imply courage and devotion? Is it too much to demand that men and women co-operate in a mutual effort to preserve their own integrity or does self-gratification take precedence over self-esteem? Self-control or intellectual discipline is not a trait peculiar to any religion but a rule taught and adhered to by those persons past and present who are the leaders in their fields or chosen profession.

Once the bill is passed, and herein lies the unseen danger, the remaining barriers of normalcy will have been lifted and promiscuity will be the keynote of a modern society. Advice

will be sought not only by those in ill health but by all and sundry who seek to follow the lines of least resistance. As it is unnatural to deprive a person of the right to conceive, so it is in contradistinction to the laws of nature to dispense advice frustrating its most sacrosanct privilege.

FREDERICK W O'BRIEN  
Lieutenant (jg) (MC) USNR

Great Lakes, Illinois

## RESTORATION OF LICENSE

*To the Editor* At a meeting of the Board of Registration in Medicine held November 13, it was voted to restore the registration to practice medicine to Dr Samuel Greenstein, 713 Dudley Street, Dorchester, whose registration was revoked November 17, 1944.

H QUIMBY GALLUPE, M D, Secretary

State House  
Boston

## BED REST IN TREATMENT OF TUBERCULOSIS

*To the Editor* The Shattuck Lecture by Dr William Dock, which appeared in the May 22 issue of the *Journal*, is a valuable presentation and has widespread implications. The following comments apply only to the sections dealing with the circulation through the lungs. This article and others by Dr Dock on the same subject are indeed thought-provoking—I am referring to his studies on the blood supply to the lung apex in the upright and recumbent positions and the consequent effect on the incidence of apical tuberculosis and healing of this and other pathologic processes involving the apex of the lung.

Bed rest, as ordered by many physicians, and recumbent bed rest may be widely different. I have been in tuberculosis sanatoriums where most patients during the day are semi-recumbent, semiupright or upright in bed except for the total afternoon rest period of two hours. Dr Dock's reasons for flat bed rest differ from those commonly taught and printed. Cecil (*Textbook of Medicine* Sixth edition 1566 pp Philadelphia W B Saunders Company, 1943 P 290) implies that lessened respiratory activity is the important feature of bed rest and does not mention circulation. He also holds that lessened toxicity follows by reason of a decreased blood supply to the lung apex. Dr Dock reaches the same conclusion (lessened toxicity), considering that an increased blood supply allows for dissipation and control of toxic products and lessened toxicity. Another widely held belief is that apical localization occurs because of decreased aeration in this region (see Best, C A, and Taylor, N B *The Physiological Basis of Medical Practice* Fourth edition, 1169 pp Baltimore Williams & Wilkins, 1945 P 299). Dr Dock considers this to be due to an apical ischemia occurring several hours during the day when the patient is upright. I have not thoroughly investigated the literature regarding these physiologic principles.

If Dr Dock's conclusions are correct—and there is much to recommend them—they should receive wide recognition. Patients with apical tuberculosis should be directed and encouraged to spend more hours flat in bed each day. Studies should be directed toward the determination of how much semirecumbency (with pillows and back rest) can be allowed without interfering with healing of an apical lesion. With this in mind disability in months might be shortened if the patient were appreciably able to increase his daily complete recumbency time.

Another point of interest is the possibility of decreasing the incidence of tuberculosis in contacts by increasing their recumbency time. This would be a hard point to prove, possibly, but speculation might be worth while. Would thirty minutes in a flat position one to three times daily sufficiently increase the apical blood perfusion to prevent implantation with the tubercle bacillus? Would more recumbent time be necessary, or would this procedure have any value? So far, the only preventive measure has been avoidance of contacts and B C G (*Bacillus Calmette-Guérin*) vaccination in children.

Another point of interest is the occasional basal or mid-lung lesion. Could there be an anomalous blood supply in which these areas are relatively avascular?

No mention is made of the effect of various positions on the lung subjected to pneumothorax or thoracoplasty. This is important, since many of these patients become ambulatory early.

Sound physiologic principles are necessary to understand and apply sound treatment procedures. Although bed rest has long been advocated it has been for reasons other than those considered by Dr. Dock and bed rest has by no means always meant flat bed rest. This, of course, is a hard dose for many patients to take, and some effective middle of the road course can possibly be devised.

These observations are particularly pertinent now that early rising has become the fashion in numerous conditions. A great many articles recommend early postoperative rising early post-delivery rising and ambulation in cardiopathies and arthropathies. I have long hoped that some rational physiologic principles would be found to suggest early ambulation in tuberculosis, but so far no short cuts are known. If it appears that flat rest in bed is superior in healing an apical lesion the back rest and pillows should be removed.

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## BOOK REVIEWS

*Diseases of the Chest with Emphasis on X-ray Diagnosis* By Eli H. Rubin, M.D. *The Principles of Surgical Treatment* By Morris Rubin, M.D. 4<sup>th</sup> cloth, 685 pp. with 355 illustrations and 24 color plates. Philadelphia: W. B. Saunders Company, 1947. \$12.00.

The text is divided into six sections, each well illustrated and complete with a fairly comprehensive bibliography. The index and the format are good, and the quality of the paper is excellent.

The first section deals with both the anatomic and technical roentgenologic considerations of the chest, together with chapters on respiratory physiology and physical diagnosis. The material devoted to roentgenologic considerations is basic and will be less valuable to the trained roentgenologist than to one entering the field of pulmonary diseases. The portion devoted to bronchospasmometry and its clinical application is interesting, that pertaining to signs and symptoms of lung disease adds little to the classic works on this subject. The statement that lack of signs does not indicate absence of disease is, however, well taken.

In the second section acute and chronic pneumonias are discussed. Acute bacterial pneumonia is analyzed from various standpoints, and the material on viral pneumonias is well presented. Under the heading of suppurative pneumonia, the author includes lung abscess in its embolic, bronchogenic and chronic forms. Space is given to pulmonary diseases caused by the higher bacteria, fungous diseases are presented in a concise manner with an accurate description of coccidioidomycosis. Those interested in industrial lung will find the pulmonary disease of chemical and physical origin well covered, although the inclusion of beryllium lung and its effects would have made the data more complete, and post-irradiation changes are touched on but lightly.

In the third section, one hundred and fifty seven pages are devoted to pulmonary tuberculosis and its complications. This is a thorough coverage, circumventing the dogmatism that has often characterized previous publications on this subject. Public health aspects, from primary infection to the adult form of the disease, are outlined and many controversial points are discussed. Histoplasmosis in relation to pulmonary calcification, is emphasized, the indications for, and contraindications to pneumothorax and thoracoplasty, as well as criteria for the selection of patients as presented are in keeping with the advanced work on these aspects of the disease. The Mondaldi procedure for the decompression of tension cavities is described and the conclusion drawn that the chief value of the operation lies in the preparation for thoracoplasty in isolated cases. Extrapleural pneumolysis is mentioned only as a discarded procedure. The authors conclude that lobectomy and pneumonectomy have a "distinct but restricted place in the treatment of pulmonary tuberculosis."

The fourth section is devoted to various chronic pulmonary diseases in which the bronchi play an important role. Pneumoconiosis is well covered and roentgenograms showing the progression of disease from its early to its late stages are presented. Bronchial obstruction is considered of sufficient importance to deserve two chapters, and foreign bodies are dealt with in some detail. Bronchiectasis, which the authors believe is largely an acquired disease, is discussed from the medical and the surgical points of view, with emphasis on preventive measures. Pulmonary emphysema and bronchial asthma with their complications and sequelae are covered. It is pointed out that compensatory emphysema is prone to develop in adults after pneumonectomy and that this fact should be taken into account in the evaluation of surgery. The authors make the following statement: "Current opinion is swinging to the view that congenital pulmonary cysts are rare and the comparative frequency with which they are found in adults speaks for an acquired origin for most of them." The chapter on neoplasms deals largely with those of bronchogenic origin.

The fifth section covers affections (including neoplasms) of the mediastinum, pleura and diaphragm as well as pleural effusions, pneumothorax and heart lung disease. Of particular interest are the portions devoted to Boeck sarcoid to diseases of the diaphragm and to spontaneous pneumothorax. Pulmonary infarction is presented only briefly, considerably more space should have been given to this important subject.

The general principles of thoracic surgery are presented in the sixth section with a view to acquainting the physician with the surgical procedures, including bronchoscopy that are available and with the accepted methods of preoperative and postoperative care of the patient. A chapter is devoted to the treatment of lung abscess, empyema and bronchiectasis. It is pointed out that the old rule of no open drainage of the pleural cavity in empyema, without a fixed mediastinum still holds. A warning not to overlook the lingula of the left lung in the diagnosis and surgery of bronchiectasis is well taken. Lobectomy is Rubin's procedure of choice for benign neoplasms, and pneumonectomy in his opinion offers the only hope for eradication of bronchogenic carcinoma. In the treatment of pulmonary tuberculosis the accepted surgical operations noted are intrapleural pneumolysis, phrenic crush and thoracoplasty. Lobectomy is discussed in some detail in the section on tuberculosis.

On the whole, this is an excellent book for the student of chest disease. In one volume the authors have presented in a concise and well blended manner the anatomy, pathology, physiology, bacteriology, roentgenology, physical diagnosis and medical and surgical therapy. An important contribution is the inclusion of the newer concepts of the pathologic physiology of the chest. In placing emphasis on x-ray diagnosis, they state that they do so "from a conviction that a modern book devoted to the clinical phases of chest diseases that does not do so is of little value and that 'the radiologist will find sufficient background material [in the book] to permit the interpretation of roentgenograms with a greater insight into the nature of the condition than from books devoted primarily to the subject of radiology.'" This is true, but the further statement that "the range of illustrative material is sufficiently diverse to constitute a working library for students of diagnostic roentgenology" is debatable.

*Curare: Its history, nature and clinical use* By A. R. McIntyre, Ph.D., M.D. 8<sup>th</sup> cloth, 240 pp., with 23 illustrations. Chicago, Illinois: The University of Chicago Press, 1947. \$5.00.

Curare, long familiar in the physiologic laboratory has recently come into prominence clinically in the treatment of tetanus, epilepsy, chorea and hydrophobia as a means of prevention of trauma in shock therapy and as an anesthetic agent. It has also been used in the diagnosis of myasthenia gravis and in the treatment of poliomyelitis. The whole subject — including the physiologic state of the drug, the pharmacologic analysis of the various components of curare and its value to medicine — is clearly set forth in this monograph. Particular attention is paid to the interesting history of the drug, but adequate consideration is also given to the chemistry of curare and the physiologic experiments used to elucidate its action. Reference is made to a standardized preparation of curare which has been developed as Intocostin. The text is ac-

accompanied by an adequate bibliography and a good index. That curare has a value as an adjuvant to anesthesia and in protecting the patient from injury in shock therapy is well established.

*A History of The American Medical Association 1847 to 1947* By Morris Fishbein, M.D. With *The Biographies of the Presidents of the Association* By Walter L. Bierring, M.D. And with *Histories of the Publications, Councils, Bureaus and Other Official Bodies* 4°, cloth, 1226 pp., illustrated. Philadelphia: W. B. Saunders Company, 1947. \$10.00.

In connection with the celebration of the centennial of the American Medical Association, the editor of the *Journal of the American Medical Association* has written a chronological history, setting forth the facts in a correct and orderly manner. Accompanying this text, which covers over five hundred pages, are biographical sketches of the various presidents of the American Medical Association by Dr. Bierring and the recipients of the Distinguished Service Medal. These in general are well written and many facts regarding the earlier presidents have been assembled in this book—material previously difficult of access to medical historians. The volume also contains a record of the councils, bureaus and various publications of the American Medical Association. There is an index of both persons and subjects.

As a reference book this volume is of value. Presumably, the facts are accurately given. Some material, however, is poorly presented, and a considerable number of illustrations are unworthy of both the publisher and the organization sponsoring the volume. Printed on heavy coated stock, the book weighs more than six pounds. It can hardly be called a highly successful venture in publishing. This is all the more surprising in view of the well known firm over whose imprint this volume is issued. Although a "must" item for every medical library throughout the world, the book, because of its format and general appearance, will have little appeal to the average physician.

*The Physical Background of Perception: The Waynflete lectures delivered in the College of St. Mary Magdalen, Oxford, in the Hilary Term 1946* By E. D. Adrian, O.M., F.R.S. 8°, cloth, 95 pp., with 21 illustrations. New York: Oxford University Press, 1947. \$3.25.

Professor E. D. Adrian, a pioneer in the investigation of brain function, summarizes his views on the transmission of the nerve impulse in the peripheral nerves, the sense organs and the brain. Nervous communication appears to be of a relatively simple character, being based on the transmission of repeated waves of activity. These brief disturbances are always made up of the same sequence of physical and chemical changes and, because they are accompanied by small electrical currents, records to show what signals are passing from moment to moment can be made. The electroencephalogram of Berger discloses a 10-per-second rhythm in the brain, associated with the inattentive state, in regions that are playing no part in mental activity because the attention is directed elsewhere. The electrical effects reveal something about the shift of attention but nothing about the way in which the implications of the picture projected on the cortex are recognized.

Thus, many of the problems raised by Adrian have no immediate solution. At present, the picture of mental activity is far from satisfactory.

This book, written in the form of lectures, is a cogent disclosure of present views on brain and mind. No conclusions are reached, and none are justified. The report is one of progress, not a final rendering. As such, Adrian's concise account is highly commendable.

*Histopathology of the Ear, Nose and Throat* By Andrew A. Eggston, M.D., and Dorothy Wolff, M.A., Ph.D. 4°, cloth, 1080 pp., with 505 illustrations, 28 plates and 9 tables. Baltimore: Williams and Wilkins Company, 1947. \$18.00.

From the title of this book one would not expect to find such a wealth of information pertaining to the ear, nose and throat. The authors have approached the study of histology and pathology of these structures in a most interesting manner. Anatomy, both gross and applied, as well as physiology, is discussed. The bibliography is complete, so that the reader may refer to original articles for more detailed discussion of any subject that he may be particularly inter-

ested in. The material, concerning subjects for which the authors are well known for their original contributions, is well presented and described.

The book is most unusual in its departure from the style of other works on histopathology because of its being so comprehensive. It will be particularly appreciated by the otolaryngologist, who will not find it necessary to delve through numerous volumes to find the information concerning the ear, nose and throat that he wishes.

The illustrations are good and supportive to the text.

It would be unreasonable to assume that some chapters could not be improved upon in some passages, but this criticism in no way detracts from the over-all value of the content. The volume is particularly recommended to residents, specialists and teachers in otolaryngology. Those who contemplate certification by the national boards will find the book invaluable. No institution with a department of ear, nose and throat should be without it.

## BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

*Concise Anatomy* By Linden F. Edwards, Ph.D., professor of anatomy, Ohio State University. 4° cloth, 548 pp., with 324 illustrations. Philadelphia: The Blakiston Company, 1947. \$5.50.

*Hypnotism Today* By Leshe M. Lecron, B.A., consulting psychologist and psychotherapist, and Jean Bordeaux, M.A., Ph.D., consulting psychologist and psychotherapist. With a foreword by Milton H. Erickson, M.D., director of psychiatric research, Wayne County Hospital, Eloise, Michigan. 8°, cloth, 278 pp. New York: Grune and Stratton, 1947. \$4.00.

*Signs and Symptoms: Their clinical interpretation* Edited by Cyril M. MacBryde, M.D., assistant professor of clinical medicine, Washington University School of Medicine, and assistant physician, Barnes Hospital, St. Louis, Missouri. 4°, cloth, 439 pp., with 74 illustrations and 6 plates. Philadelphia: J. B. Lippincott Company, 1947. \$12.00.

*Rhinoplasty and Restoration of Facial Contour: With special reference to trauma* By Jacques W. Maliniac, M.D., clinical professor of plastic reparative surgery and associate attending plastic surgeon, New York Polyclinic Medical School and Hospital, and attending plastic surgeon, Sydenham Hospital, New York City. 8°, cloth, 327 pp., with 214 illustrations. Philadelphia: F. A. Davis Company, 1947. \$7.50.

*Human Gastric Function: An experimental study of a man and his stomach* By Stewart Wolf, M.D., assistant professor of medicine, Cornell University Medical College and New York Hospital, and Harold G. Wolff, M.D., associate professor of medicine, Cornell University Medical College and New York Hospital. With a foreword by Walter B. Cannon, M.D. (Oxford Medical Publications). 8°, cloth, 262 pp., with 55 illustrations. New York: Oxford University Press, 1947. \$5.00.

## NOTICES

### ANNOUNCEMENT

Dr. Bernard M. Jacobson announces the removal of his office for the practice of internal medicine to 422 Beacon Street, Boston.

### PHI DELTA EPSILON LECTURE

Dr. Frank H. Lahey, of the Lahey Clinic, will discuss "Hyperthyroidism and the Antithyroid Agents," at a lecture sponsored by the Tufts Chapter of Phi Delta Epsilon, held in the amphitheater of the Beth Israel Hospital on Wednesday, January 14, at 8:30 p.m. Interested physicians and medical students are cordially invited to attend.

(Notices continued on page xiii)

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## DIARRHEA OF THE NEWBORN\*

### Its Causes and Prevention

STEWART H. CLIFFORD, M.D.†

BOSTON

A REVOLUTIONARY change in social custom concerning childbirth has occurred during the past decade. Local evidence of this change is afforded by the statistics from the Boston Lying-in Hospital. This hospital delivers about 20 per cent of the infants born in Boston each year. The total number of babies delivered in this institution in 1935 and in 1945 was about the same—4530 and 4685, respectively. In 1935 there were 1015 home deliveries in the outpatient department—in 1945 there were but forty-seven home deliveries, and in 1946 there were none.

The virtual disappearance of home births was not reflected in a corresponding increase in the deliveries on the wards of the hospital. In 1935 there were 2762 ward births, and in 1945 there were 2236.

What, then, happened to the missing 1500 patients? The hospital statistics furnish the answer to this question; these patients demanded private physicians and private ward care, and they were delivered on the private side of the hospital. Richardson House, originally designed to accommodate 900 patients, saw the birth of 753 infants in 1935 and 2401 in 1945.

There can be but one answer to this phenomenon: the public is convinced that the safest place for a mother to have her baby is a maternity hospital. So far as the mother is concerned, statistics have proved the public to be right, for the maternal mortality is reaching an all-time low; it remains to be proved whether the hospital or the home is the safest place for a newborn infant. Evidence submitted from New York City demonstrates that there is at present a persistently upward trend in the death rates from diarrheal disorders in the neonatal group of infants.<sup>1</sup> This increase is due in great

measure to the prevalence of epidemic diarrhea of the newborn.<sup>1</sup>

### CAUSES OF EPIDEMIC DIARRHEA OF THE NEWBORN

It is significant that the literature on epidemic diarrhea of the newborn has appeared only during the past fifteen years. The appearance of this syndrome as a public-health problem coincides with the shifting of the scene of childbirth from the home to the hospital.

Countless factors have contributed to making the newborn infant in a lying-in institution extremely vulnerable to all types of infection. The combination of an increased birth rate and increased hospital births has led to the mass overcrowding of babies in nurseries. Shortage of personnel in the face of increased demands has resulted in a breakdown in nursery and formula-room technique.

Out of his long experience as a hospital consultant Pollock<sup>2</sup> observes the tendency of architects and consultants to fail to provide adequate space for nurseries. He found that "all too frequently nurseries are assigned to what might be designated as left-over space and their size is determined by the number of bassinets that can be crowded in without any regard to spacing or the aisles between them."

A review of the literature clearly indicates that the syndrome described as epidemic diarrhea of the newborn is not a pathologic entity but a miscellaneous group of cases of various etiologies, known and unknown, bound together by a common symptom—diarrhea.

The reported epidemics can be divided into three groups. In the first, evidence of a bacterial origin is present, although the organisms discovered frequently belong to groups not ordinarily considered pathogenic, the infecting agent apparently enters the nursery via an adult carrier and reaches the infant by the fecal-oral route through a break in the nursery or formula room technique. The second group

\*Presented at the annual meeting of the Massachusetts Medical Society, Boston, May 21, 1947.  
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includes the epidemics in which a virus etiology has been proved or strongly suspected with the backing of certain presumptive evidence. The large and controversial third group comprises outbreaks in which etiologic studies on the stools have failed to demonstrate an inciting agent.

#### EPIDEMICS OF BACTERIAL ORIGIN

A significant investigation into the cause of recurrent outbreaks of epidemic diarrhea of the newborn in a Kansas Hospital has been reported by Ensign and Hunter,<sup>3</sup> whose approach was based on a knowledge of the method of spread of the infection rather than on a bacteriologic search for specific organisms. From June to October, 1945, six outbreaks of diarrhea had occurred in the hospital nursery, during the same period more than 400 cases of diarrhea in adults had occurred in the community. Prior to each of five hospital outbreaks, one mother or nurse on the obstetric floor had developed the disease. In the sixth outbreak the mother had had the disease shortly before entering the hospital. In every case in which the mother had the disease her infant developed it. The nurseries were crowded and there was a shortage of personnel. The authors reasoned as follows:

The outbreaks could be easily explained on the basis of secondary infection from infected mothers or nurses if we keep in mind a well-known fact in the epidemiology of gastrointestinal disease, namely, that apparently healthy persons who have ingested organisms are carriers of those organisms until they are eliminated from the alimentary canal. These organisms may be eliminated in one or two days. Nevertheless, until they are eliminated, persons harboring them are temporary carriers capable of passing the infection on to others. The only condition which could result in a large group of temporary carriers is a recent ingestion of contaminated food or water.

Their investigations proved that the milk supply of the entire community was grossly contaminated with *Bacillus pyocyaneus* (*Pseudomonas aeruginosa*) at the dairy and that the milk was then not sufficiently pasteurized. Bacterial counts on the milk disclosed over 3,000,000 organisms per cubic centimeter. *Ps. aeruginosa* was isolated from all infants' stools cultured, from autopsy material, from nurses' stools and from the milk supply.

McClure<sup>4</sup> reports four different hospital epidemics of diarrhea of the newborn in the Province of Ontario. In Hospital "A" two outbreaks occurred. In the first of 62 infants, 26 became ill, and 3 died. Hemolytic *Escherichia coli* was found in the stool cultures of 14 of 16 infants and also in the nursery supervisor's stool culture. In the next outbreak, which involved 31 infants with 7 deaths, eight stool cultures were made, and seven showed hemolytic *Esch. coli*. Stool cultures of 16 normal infants were negative. Cultures in 4 of 17 nurses showed hemolytic *Esch. coli*. The milk formula showed a high bacterial count, with nonhemolytic *Esch. coli*. Cultures from the top of the common bathing table showed hemolytic *Esch. coli*. Six of the hemolytic

*Esch. coli* strains from the infants, bathing table and a night nurse were identical by sugar reactions. Another strain from an infant and one from a nurse were identical.

In Hospital "B" the epidemic was dated from the time a mother and her infant developed diarrhea. Seven infants became ill, and 1 died. Subsequently, stool cultures on 12 healthy babies in the nursery revealed hemolytic *Esch. coli* in 7. In Hospital "C" 12 infants developed diarrhea, and an abundant growth of hemolytic *Esch. coli* was obtained from evaporated-milk formula and nipple jars. In Hospital "D" a severe epidemic occurred, 18 infants had the disease, and 12 died. Hemolytic *Esch. coli* were obtained from the stools of 8 of 11 sick infants and from 2 of 18 healthy infants. In their investigation the authors found the nursing technic in all these hospitals very faulty—the diapers were rinsed in the same nursery sink in which the formula bottles were subsequently warmed. Milk was stored on the wards in quart stock bottles from which the individual bottles were filled at feeding time.

Baker<sup>5</sup> reported three epidemics of diarrhea of the newborn occurring between 1935 and 1938 in one New York Hospital. The first outbreak involved 59 infants in the obstetric nurseries. Various organisms were grown on stool culture but not consistently enough to be thought significant. These organisms included *Esch. coli mutabile*, hemolytic *Staphylococcus aureus*, *Staph. albus*, *Bacillus subtilis*, *Esch. coli*, alpha-hemolytic streptococcus, gamma-hemolytic streptococcus and *Aerobacter aerogenes*. The second outbreak involved 13 premature infants. Cultures of the stools of 9 patients revealed *Esch. coli mutabile* or hemolytic *Esch. coli* organisms, which some workers have regarded as pathogenic. The author quotes Dulaney, who found *Esch. coli mutabile* in the stools of 67 per cent of patients in an epidemic of diarrhea of the newborn. In the third outbreak involving 13 infants, no suspicious stool organisms were isolated.

McKinlay<sup>6</sup> described an epidemic involving 6 infants with 2 deaths apparently caused by an organism of the *Salmonella* group. She found a nurse as the probable carrier of the infection. Bloxson<sup>7</sup> reported an epidemic of infectious enteritis in Houston, Texas, with a mortality of 50 per cent. Stool cultures in 18 cases revealed organisms of the *Salmonella* group in 5. Abramson et al.<sup>8</sup> discussed an epidemic of diarrhea in the newborn due to *Salmonella* infection. Cummings<sup>9</sup> observed a nursery outbreak in Michigan caused by *Salmonella Panama*, with 12 deaths. Diarrhea had been rampant six months prior to the epidemic studied and had occurred sporadically in the interval. *S. Panama* was recovered from the stools of a graduate nurse, a nurse's aide and a maid.

Jampolis and his colleagues<sup>10</sup> have reported an epidemic due to *Klebsiella pneumoniae* (*Bacillus*

*mucosus capsulatus*) This infection was traced to 3 nursery maids

Schwentker<sup>11</sup> described an epidemic of diarrhea from Baltimore in which there were 21 deaths. *Bacillus dysar* was recovered from the stools of 36 infants

Wheeler and Foley<sup>12</sup> isolated Lancefield Group D streptococci in an outbreak in Boston, with epidemiologic and clinical studies that suggested respiratory or air-borne transmission. The authors make the important observation that Group D streptococci may be of pathogenic significance in infants. They point out that beta characteristics are not specific for this group of streptococci. Alpha, beta, and gamma strains were encountered in all serologic types of Group D organisms — "a fact which invalidates many earlier and more extensive attempts to determine the incidence of the various serologic groups of streptococci in normal infants"

The preceding review of recorded outbreaks of epidemic diarrhea demonstrates several points: the epidemics may be caused by a diversity of organisms, the newborn infant appears to be very susceptible to infection with organisms not ordinarily considered pathogenic, any infant fed milk or fluid from a bottle is peculiarly vulnerable to infection because the same person who feeds him and handles the nipples also handles the diapers and the infant's excreta, and it is well known that efficient scrubbing is required to free the hands and fingernails of bacteria of fecal origin, and many of the epidemics can be traced to carriers in the nursery personnel, infection by this fecal-oral route constituting ample evidence of faulty nursing technique

#### EPIDEMICS OF VIRUS ETIOLOGY

A virus etiology for certain outbreaks of diarrhea in the newborn has been suspected from the first. However, the evidence for a virus infection has been chiefly negative, many epidemics having received most careful epidemiologic and bacteriologic investigations without the discovery of a specific etiologic organism. The infants in these outbreaks frequently exhibit a normal or lowered white-cell count and fail to respond to chemotherapy

Lyon and Folkow<sup>13</sup> described three epidemics in 1926, 1934 and 1938 that suggest the virus of influenza as a possible etiologic agent, since at the time of each epidemic clinical influenza infection was present in the community

In 1943 Campbell<sup>14</sup> reported from Melbourne outbreaks occurring in three hospitals at the same time that epidemic cases of so-called "gastro flu" were common in the city. In 1944 a severe epidemic of diarrhea of unknown etiology in the newborn was observed in Philadelphia by High, Anderson and Nelson,<sup>15</sup> occurring at the same time as an epidemic of diarrhea, nausea and vomiting of unknown cause in adults

The first positive evidence that a filterable virus was a cause of certain epidemics of diarrhea of the newborn was submitted by Light and Hodes.<sup>16</sup> Two epidemics were studied in 1941, and stool filtrates tested in a variety of small animals, with negative results. In 1942 two epidemics in Baltimore and two in Washington were studied. In each of the four epidemics pooled stools, Seitz-filtered in three and unfiltered in one, were given nasally to young calves. In two to five days all the animals developed a bloody, mucoid diarrhea that lasted an average of three weeks. Successive calf passages were easily made with each of the four strains. Cross-immunity studies indicated that the four strains represented a single agent.

After recovery the calves had developed immunity and large doses of active material failed to cause disease. Serums obtained from 6 infants after convalescence conferred complete or partial protection against the nasal injection of active material. The virus was not inactivated until the material had been boiled for ten minutes or exposed to a temperature of 80°C (170°F) for an hour.

Cummings<sup>9</sup> is convinced that he was able to recover, in an epidemic of diarrhea of the newborn, a filterable agent of the type described by Light and Hodes, although he was unable to maintain the potency of this agent beyond the fifth calf transfer. This epidemic involved 22 babies. Nose, throat and stool specimens were obtained free from bacterial pathogens. Pooled material was tested for viruses in mice, monkeys, guinea pigs, chicks, cotton rats, chick embryos, hamsters, newborn pigs and newborn calves. All the animals or mediums reacted negatively except the calves.

In October 1943 Buddingh and Dodd<sup>17</sup> observed one of a pair of twins to have stomatitis and diarrhea. Within the next two weeks and in spite of strict isolation precautions 16 of 30 infants in the nursery developed diarrhea, with a mild stomatitis in 10. In contrast with other epidemics of diarrhea of the newborn this outbreak was relatively mild, with no fatal cases. With an inoculum of stools obtained in this epidemic the authors were able to produce lesions on the scarified cornea of rabbits. The agent was readily filterable through Berkefeld V candles. Strains of the agent were maintained for as many as forty-five serial passages. Immunity developed in the rabbit eye in a period of three weeks. Serum obtained from 12 patients during the acute disease produced positive results when mixed with the virus, similar mixtures using serum obtained during convalescence caused no lesions. Attempts to propagate the virus in other animals or in the developing chick embryo were unsuccessful. The filterable agent has been isolated by Buddingh<sup>18</sup> from stools obtained in epidemics in Nashville, Memphis, Cincinnati and Boston. Cross-immunity has been demonstrated between all strains regardless of whether the death rate in an epidemic was 0 or over 50 per cent. It has not been possible

to determine whether the viruses isolated by Light and Buddingh are the same. It seems probable that a virus is the usual etiologic agent in epidemic diarrhea of the newborn, but, as in encephalitis, different viruses may be concerned in different epidemics.<sup>11</sup>

Cummings<sup>9</sup> and the group studying diarrhea and enteritis in Michigan encountered an epidemic of diarrhea in the premature section of a children's hospital. Because newborn calves were not available at the time, the material obtained was tested on smaller animals with negative results and on the rabbit's cornea after the method of Buddingh and Dodd. The Seitz filtrates of pools of infants' stools gave positive eye reactions. However, subsequent experience with serial passages of corneal material led the group to conclude that the reaction was erratic if not nonspecific. They tested a large number of rabbit corneas with trauma, trauma and alundum, stools and mouth washings from normal infants and various bacteria and found it possible with all these specimens or technics to produce what they considered to be typical positive eye reactions as described by Buddingh and Dodd.

Cummings's conclusion that Buddingh's rabbit-eye scarification test is not specific for the virus of epidemic diarrhea is a great disappointment to all workers in the field. This simple method of proving a virus etiology in an epidemic under investigation had been expected to clarify much of the present confusion surrounding this syndrome. At present the test must be shelved until other investigators prove its exact status.

The lack of a relatively simple technic to identify the virus of this disease is the greatest handicap to further progress. Both Light and Hodes and Cummings agree that the virus can be grown and studied in newborn calves. This method is of limited usefulness in actual practice. Light and Hodes have reported but one experiment based on four outbreaks, whereas Cummings, with his elaborate study group financed jointly by the Kellogg Foundation and the Michigan Department of Health Laboratory in a four-year study of many epidemics of diarrhea, has only reported the use of calves in testing the material from one epidemic.

Since we cannot at the moment accept the epidemics reported by Buddingh and Dodd as having a proved virus etiology, the only positive evidence is found in the four epidemics reported by Light and Hodes and the one reported by Cummings.

#### EPIDEMICS NOT ASSOCIATED WITH THE USUAL BACTERIAL PATHOGENS

The epidemics of diarrhea in the newborn in which no virus etiology has been demonstrated and in which none of the usual bacterial pathogens have been found constitute by far the largest group reported in the public press and in the medical literature and by public-health officials studying the problem.

An epidemic involving 32 infants with a high mortality was described in 1936 by Barenberg, Levy and Grand<sup>19</sup> in which no specific etiology could be found but in which the authors suspected that either a virus or certain toxins of the colon bacillus were responsible. Rice et al.<sup>20</sup> analyzed eleven outbreaks of highly fatal diarrhea in New York City between 1934 and 1936 in which no inciting agent could be discovered. In a subsequent paper in 1939 Frant and Abramson<sup>21</sup> confirm the negative pathological and bacteriologic findings and point out that diarrhea of the newborn epidemiologically exhibits the characteristics of a highly virulent communicable disease. They suggest that these infections were not reduced because of certain inherent deficiencies in present methods of obstetric, pediatric and nursing care of the newborn — the modern mass care of newborn babies in open nurseries may even promote the rapid spread of infection.

Outbreaks occurred in 1940 in three widely separated English cities with a case mortality of 29 per cent. No specific etiology could be discovered, but Ormiston<sup>22</sup> believed that the cause might be a virus or systemic infection or a general metabolic disturbance leading to the proliferation of any pathogenic or potentially pathogenic organism that happens to be present in the bowel.

Epidemic diarrhea occurred in San Francisco in 1942 and 1943, and Geiger and Sappington<sup>23</sup> reported 324 cases with 45 deaths. Although no specific etiology was found there was marked overcrowding in almost every nursery, as well as lowered standards of nursing care.

Weymuller, Beck and Ittner<sup>24</sup> describe an outbreak of epidemic diarrhea involving 19 infants with no deaths. A very carefully thought out prophylactic technic had been in successful operation from 1937 to 1945, when, because of a shortage of nurses, the technic was necessarily violated, and the authors believe that the epidemic was the result.

Rubenstein and Foley<sup>25</sup> reviewed nineteen outbreaks of epidemic diarrhea of the newborn of unknown etiology reported to the Massachusetts Department of Public Health from 1935 to 1945. In all, 258 cases were reported, and 85 patients died. Their investigations revealed almost unbelievable breaks in nursing and formula-making technic. Although the practice was in direct violation of existing regulations, 7 nurseries used a common rectal thermometer. The thermometers were supposedly sterilized by soaking in a bichloride or alcohol solution. Bacterial counts on samples of one of these thermometer dips revealed 7,000,000 viable microorganisms per cubic centimeter, mostly *Esch coli*. A sample of dip from another nursery revealed 44,000 organisms, the majority being *Esch coli*, *Proteus vulgaris* and *Staph albus*. Several nurseries used common oil bottles instead of the recommended individual cups. In many nurseries nurses dip their hands in so-called "sterilizing" solutions. Bacterial

counts on two of these dips, one bichloride and one alcohol, revealed 75,000 and 150,000 organisms per cubic centimeter, including *Staph aureus*, *Esch coli*, alpha streptococcus, Lancefield Group D streptococcus and *B subtilis*.

Adequate space was available in only 3 nurseries, and the nursery staffs were considered adequate in only 3. In 6 of the 10 hospitals formula preparation was not adequately supervised. Samples of formulas from several nurseries gave bacterial counts of 9500, 32,000 and 396,000 per cubic centimeter, the identified organisms being alpha streptococcus, Lancefield Group D streptococcus, *Esch coli*, *Staph. albus*, *Pr vulgaris* and *B subtilis*. Examinations of nipples revealed the presence of large numbers of organisms. One supposedly sterile nipple and one funnel produced a pure culture of *Staph aureus*.

Cummings<sup>9</sup> and his study group made similar discoveries regarding nursery practice in Michigan. In investigating a number of outbreaks of neonatal diarrhea with stool cultures that were negative for the usual pathogenic organisms, Cummings became interested in the variety of organisms that were identified and he began to speculate on their etiologic significance. The bacteria isolated included coagulase-positive staphylococci, hemolytic streptococci, various strains of *Proteus*, *Shigella alcalescens*, *Bacterium alcaligenes* (*Alkaligenes faecalis*) and various coliform organisms. These organisms were also routinely recovered from the various supplies, equipment and solutions of the nurseries. In one nursery *Bact alcaligenes* was isolated from twenty-four stool specimens, fifteen meconium specimens, one infant nose speculum, three nurse stool specimens and three nurse's-side stool specimens. It was also isolated from nursery basins, enema solutions, subcutaneous saline solutions, soap solutions, table-tops and handbrushes. The conclusion was as follows:

It has gradually become the opinion of the study group that this type of outbreak is due to massive bacterial contamination with organisms usually considered to be of low or absent pathogenicity together with a complete absence of the usual nursery techniques. It is felt that filth in the nursery is the principal contributing factor.

From Rochester, New York, comes a report by Lembecke, Quinlivan and Orchard<sup>10</sup> of two outbreaks of epidemic diarrhea of the newborn that occurred within a four-month period of 1942. The epidemics were controlled by studies on the mode of transmission. The first outbreak affected 28 of the total of 50 infants, with 3 deaths, and was believed to have been transmitted by contaminated rubber nipples and formulas and to a lesser extent by indirect contact. The nurseries were understaffed, babies were diapered before being fed, the hand washing was very perfunctory in cold or tepid water, with very little soap. The rubber nipples were boiled for less than twenty minutes, with some of the nipples float-

ing on the surface, and formulas were inadequately sterilized. Four formula cultures and twelve nipple cultures revealed organisms of the colon bacillus group, presumably of fecal origin. In the second epidemic breast-fed infants were chiefly attacked. Again, infants were diapered prior to feeding, and there was faulty technic in both hand and breast washing.

It is thus readily seen that the reported outbreaks of epidemic diarrhea of the newborn in which no etiology could be established can also be subdivided into two groups. The first consists of outbreaks in nurseries with excellent technics where careful investigation of the affected patients and of their environment by both bacteriologic and epidemiologic studies fail to reveal an etiologic agent, in these outbreaks the negative evidence suggests a virus etiology. In the second and by far the largest group, investigations by trained epidemiologists and bacteriologists failed to reveal a specific organism, but such atrocious nursery and formula-room technic was uncovered that infection with anything was possible. As suggested above the epidemic may even have resulted from massive bacterial contamination with organisms of low or absent pathogenicity.

#### PREVENTION

It is evident that diarrhea of the newborn can be caused by a variety of infections. When the services of trained epidemiologists and bacteriologists with adequate laboratory facilities are available, investigation of an epidemic may quickly reveal a specific etiologic agent. When these facilities are not available or if available are not called on, an epidemic may well pass without etiologic diagnosis. Recorded experiences have reported *Pseudomonas aeruginosa*, *Esch. coli mutabile*, hemolytic *Esch. coli*, organisms of the Salmonella group, *K pneumoniae*, *S dysenteriae* (Sonne) and Lancefield Group D streptococcus as having been the probable cause of certain epidemics of newborn diarrhea. From the point of view of prevention the presence of these organisms indicates a breakdown in nursery technic that permits carrier-fecal-oral infection of the newborn.

There can be little doubt that virus infection can produce epidemic diarrhea in the newborn. There is suggestive evidence that certain viruses, presumed to be the agent of widespread disease in the community, may also be the cause of coexisting epidemic diarrhea in the local nurseries. There is positive evidence that five epidemics have been caused by a specific virus. In other epidemics there is suggestive evidence for a specific virus etiology in the tendency of diarrhea to spread in the pediatric wards after the baby from a nursery epidemic is admitted for treatment, in contrast to the lack of spread when the infant's infecting organism belongs to the Salmonella or dysentery group. In the absence of a practical method of demonstrating the presence of

a virus in a given epidemic it is impossible to know how many or how few epidemics now classed as of unknown etiology are of specific virus etiology

The discovery of a practical method to identify and study the specific virus of epidemic diarrhea would be one of the greatest advances in modern pediatrics. It is quite apparent that such a discovery would be of inestimable value in controlling the occasional outbreak of this disease in the obstetric nursery of healthy infants. What is not so generally appreciated is that this disease is not confined to newborn nurseries and that it is endemic in infants' hospitals, where it constitutes a great and perennial problem, the solution of which may well hinge on the discovery of such a method of study.

The etiologic importance of a specific virus in certain outbreaks cannot be overemphasized but at the same time it is well to point out that before negative evidence of a virus etiology can be considered, the epidemiologic and bacteriologic investigations must satisfy the highest standards. Whenever trained public-health officials have investigated numerous epidemics of supposedly unknown etiology, whether the investigations took place in Massachusetts, Michigan or New York, the investigators have uncovered such unbelievably poor nursery and formula-making technic that it has been unnecessary to fall back on an unknown virus to explain the epidemic.

Physicians who have the responsibility of caring for newborn infants in the large and small hospitals throughout the land must set about preventing epidemics of diarrhea whose causes are known. Care of the newborn must be altered so that a baby is not fed a formula containing 396,000 bacteria per cubic centimeter from a nipple covered with a pure culture of staphylococci with hands bearing *Salmonella*. The nursery staff must be as alert to the dangers of diarrhea in the newborn as the obstetric staff is to the dangers of the hemolytic streptococcus infection in the mother. No nurse with scarlet fever would think of going into the delivery room, and yet a colleague investigating an outbreak of diarrhea in a distant city found a nurse who stated that just prior to the outbreak she had had such a severe diarrhea that she had been forced to spend more time out of the nursery than in it. Perhaps, when these glaring breaks in technic have been controlled, the protection thus afforded may well block the spread of virus infection as well.

The long-term protection of mothers and newborn infants in lying-in institutions demands an extensive national program of new hospital construction. In some hospitals in this country mothers are placed on cots in corridors, and the average stay in these hospitals for mother and child is forty-eight hours. In either new construction or the remodeling of old hospitals primary attention must be given to the needs of the newborn infant. Ideally, each infant should have a private room, or a mother and her

infant should share the same room. Certainly, the massing of infants in one nursery should be avoided. The present compromise suggested is that the maximum number of babies assigned to one nursery unit should be the number from six to twelve that can be attended by one nurse.

The following basic principles underlying the control of infection in newborn nurseries that must be satisfied by a successful nursery technic are relatively simple.

*Block air-borne infection, both that acquired at short range by droplet transmission and that acquired from pathogenic organisms diffusely distributed throughout the air*

The requirement that each infant in the nursery be provided with 300 cubic feet of air space, or 30 square feet of floor space,<sup>27</sup> is an attempt to protect the infant from air-borne infection by the dilution factor. Many existing hospitals would find it a physical impossibility to satisfy this requirement. The same dilution factor could be provided an infant in half the floor space if the air-circulation rate were doubled. Chapple<sup>28</sup> has reported that recent experience has demonstrated that the air in the nurseries can be sterilized by ultraviolet radiation and by the evaporation of propylene glycol to a strength of 1 5,000,000 in the air (a continuous evaporation of approximately 0.01 cc of propylene glycol per cubic foot in a still nursery). The bacterial count in the air can be reduced by the use of an oil film on the floor and by oil-impregnated blankets and linen. It should be apparent that 30 square feet per infant should not be accepted as a fixed requirement when other solutions may be even more efficient.

The control of droplet infection is a more difficult matter, many believe that the ordinary mask is most inefficient. If masks are to be relied on they should be of the deflection type or made of thick layers of nonabsorbent cotton.

For nurseries with limited available space, for isolation nurseries and for premature-infant nurseries an incubator of the Chapple type may be the solution. In this incubator the infant is surrounded by conditioned fresh air drawn directly from outdoors and is further protected from all droplet infection through being completely inclosed in the incubator.

*Block infection acquired from the ingestion of pathogenic organisms contained in food or fluid*

This problem is the easiest of all to solve through the terminal unit sterilization of the formula or fluid in the bottle, with the nipple attached and covered.

*Block infections acquired from physical contact between the infant and infected personnel or material*

Cummings<sup>9</sup> and his group were able to prevent this type of infection through expert nursing supervision, adequate nursing personnel, infection control among nursery personnel and mothers, carrier control among nurses and mothers, isolation of infected infants, hand technic, sterile supplies and visitor control.

One physician should be appointed as chief of the nursery service with the responsibility and authority for maintaining the standards for the care of all newborn infants, public and private.

It is fortunate that each hospital is not forced to work out for itself the details of standards and recommendations for the nursery care of their full-term and premature infants. The Children's Bureau, in co-operation with an advisory committee of obstetricians and pediatricians and with the help of the Committee on the Fetus and Newborn Infant of the American Academy of Pediatrics, have prepared and published standards and recommendations<sup>10</sup> that, if adopted so far as possible by every hospital attempting infant care, would satisfy the basic principles mentioned and go a long way toward removing the hazard of epidemic diarrhea in the newborn.

All who have been given the grave responsibility of the newborn nurseries in lying-in institutions know that sooner or later, for one reason or another, one or more of their infants may develop diarrhea. The entire literature is in agreement regarding how this situation should be handled.<sup>2, 11, 12, 13, 14, 15</sup> If 1 infant develops diarrhea he should be instantly isolated in an isolation nursery until the significance of the situation can be judged. Should 2 infants from the same nursery develop diarrhea, both babies must be isolated and the nursery quarantined until all contacts have been discharged and the nursery cleaned and made ready for new admissions. With the declaration of the quarantine a mobile nursery should be set up in an available room into which all freshly delivered patients shall be admitted. If 3 infants from the same nursery develop diarrhea the syndrome of epidemic diarrhea of the newborn is assumed to be present, and the situation instantly reported to the board of health.

Strict adherence to this program may well limit a potential epidemic to 1 or 2 cases. The literature stresses the fact that it is disastrous to temporize with this situation.

Should a real outbreak of epidemic diarrhea occur, reported experience insists that the only way to stop the outbreak is to shut down the entire obstetric unit to all admissions until all patients are discharged.

#### SUMMARY

The emergence of epidemic diarrhea in the newborn as a public-health problem coincides with the transfer of the scene of childbirth from the home to

the hospital. Hospitals have been unprepared for this migration, and the mass crowding of infants in nurseries, in addition to the shortage of personnel, has produced conditions favorable for the spread of infection. There is a national need for more obstetric beds and for more nurseries, each to be limited to 8 to 12 newborn infants.

A specific virus etiology for five epidemics has been proved. This virus is probably the cause of many other outbreaks. There is great need for a practical method of demonstrating a possible virus etiology during the progress of an epidemic of diarrhea. It is dangerous to assume a virus etiology for an epidemic on the basis of negative evidence unless the epidemiologic and bacteriologic investigation has been conducted by experts. Specific measures to control or prevent virus diarrhea can be expected to follow the discovery of practical methods to identify and study the virus.

Many epidemics of diarrhea in the newborn have been traced to a variety of pathogenic organisms that could only reach the infant by the fecal-oral route. In the greatest number of epidemics the patients have had none of the usual bacterial organisms in the stools, and yet in a large percentage of these outbreaks trained investigators have found evidence of gross breaks in nursery technic.

Without waiting for the results on future virus research the first obligation is to block all routes by which the infant can acquire bacterial infection in the nursery through a strict application of known nursery and formula-room technics. It is even conceivable that strict technic may block the spread of virus as well as bacterial organisms.

Many large hospitals caring for thousands of babies each year have demonstrated that a strict nursery and formula-room technic can, in spite of personnel shortages and crowding, protect the newborn population from outbreaks of epidemic diarrhea.

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## AN UNUSUAL CASE OF ACUTE INFECTIVE POLYNEURITIS WITH VISCERAL LESIONS\*

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THE terms "acute febrile polyneuritis," "acute infectious polyneuritis," "infectious neuritis" and "Guillain-Barré syndrome" are commonly used to designate a class of diseases that are characterized by the acute onset of an ascending flaccid motor paralysis, with loss of tendon reflexes and sensory changes in the extremities, and by elevation of the spinal-fluid protein without pleocytosis. Facial diplegia occurs in some cases and, less often, bulbar paralysis. Paralysis of respiratory muscles results in death in 10 to 40 per cent of cases, and recovery is usually complete in the survivors. The cause of the disease is unknown. Although attempts to isolate a filterable virus or a bacterial neurotoxin have been unsuccessful, an infectious etiology has been predicated because of the usual antecedent respiratory or gastrointestinal infection, the acute febrile course and the nature of the pathological changes.

At the Boston City Hospital we have encountered 3 or 4 cases of acute infective polyneuritis each year. The clinical features of 26 of these cases was the subject of a recent review by Forster, Brown and Merritt.<sup>1</sup> Owing to the high mortality (42 per cent) an opportunity has been afforded to conduct post-mortem examinations in several of them. One in particular excited our interest because of the association of polyneuritis and jaundice.

It is reported in detail because of the rarity of such cases in the medical literature.

#### CASE REPORTS

**CASE 1** The patient (BCH A44-164), a 28-year-old man, entered the hospital on February 2, 1944, because of dyspnea, orthopnea, cough and ankle edema. These symptoms had developed gradually for the previous several years and progressed in the preceding few weeks to the point where he was incapacitated for work.

At the age of 12 years, the patient had had arthritis involving both ankles and causing a deformity of the feet. In 1936, when he was 20 years of age, the deformity had been corrected by a transplantation of the extensor tendons. At that time a cardiac murmur was discovered, and for the next year he was treated by continuous bed rest for suspected rheumatic fever.

Physical examination revealed the patient to be somewhat distressed by flatulence, which was only partially relieved by frequent eructations of gas. He was orthopneic. The heart was moderately enlarged, and there was a systolic thrill over the apex. Diastolic and systolic murmurs were heard at both the base and the apex of the heart. The apical systolic murmur was harsh and blowing, and the diastolic murmur was low, rumbling and presystolic in time. The liver and spleen were not palpable.

The temperature was 98.6°F, the pulse 88, and the respirations 30. The blood pressure was 148/50.

Examination of the blood disclosed a hemoglobin of 86 per cent and a white-cell count of 16,800 that fell to normal thereafter. The differential count was within normal limits. The corrected sedimentation rate was 0.45 mm per minute. The blood nonprotein nitrogen was 65 mg per 100 cc. on admission and later 36 and 31 mg. The urine had a specific gravity of 1.032, the first three specimens gave a +++ test for albumin and the sediment contained a few red and white cells, but later specimens were normal. The vital capacity was 1.9 liters. Four electrocardiograms revealed lengthened PR interval of 0.30 to 0.38, the T waves were low, with a slightly high origin, in Lead 1 and diphasic in Leads 2, 3 and 4. These records were interpreted as "consistent with active myocardial involvement."

The patient was digitalized, and all the symptoms disappeared. He was discharged on February 25, with instructions to continue taking digitalis.

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On the 2nd day after discharge, he developed a mild discomfort in the epigastrium that rapidly increased in severity radiating to both sides of the chest anteriorly. The pain was not affected by breathing, by food or by belladonna. Repeated gaseous eructations afforded some relief. The patient was readmitted on February 28.

Physical examination showed that the patient was considerably distressed by the abdominal pain. He was oriented and rational. There were numerous small nontender axillary and inguinal lymph nodes. The heart was moderately enlarged, and the murmurs were unchanged. No signs of cardiac decompensation were present. The liver and spleen were

During the first 5 days in the hospital the abdominal pain became much less severe. The surgical consultant was of the opinion that there were no signs of peritoneal irritation or intestinal obstruction. On the 6th hospital day the patient had a sore throat, but the temperature was normal. The white-cell count at that time was 30,200 with 60.5 per cent neutrophils (52.5 per cent adult and 8 per cent band forms), 0.5 per cent eosinophils, 16 per cent small lymphocytes, 9 per cent atypical lymphocytes, 1 per cent large lymphocytes, 9 per cent young lymphocytes and 4 per cent monocytes. The blood smear was thought to be consistent with a diagnosis of infectious mononucleosis. The corrected sedimenta-

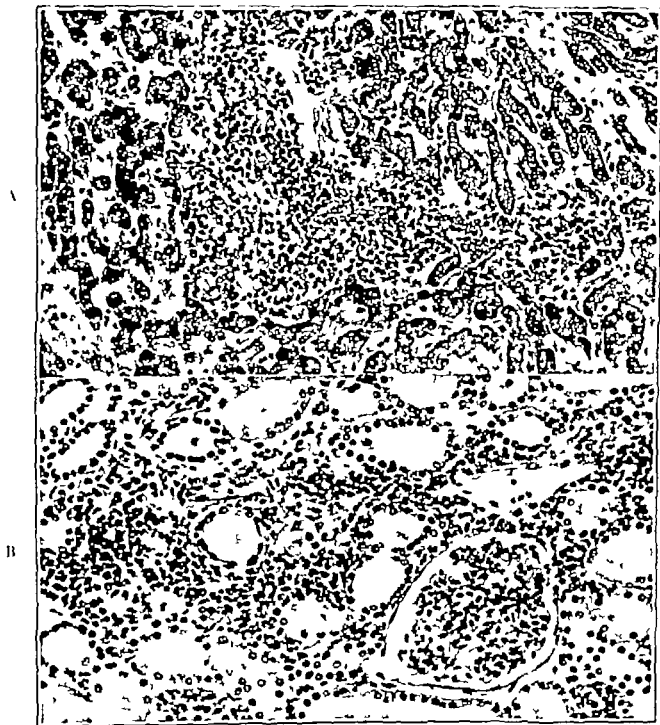


FIGURE 1. A Shows a Papanicolaou's Methylene Blue Stain of Portal Area of Liver to Demonstrate Infiltration of Lymphocytes, Plasma Cells and Unidentified Mononuclear Cells. B Illustrates a Papanicolaou's Methylene Blue Stain of the Kidney Showing Interstitial Infiltration of Lymphocytes, Plasma Cells and Rare Eosinophils.

not palpable. Neurologic examination revealed no abnormal findings.

The temperature was 98°F, the pulse 100 and the blood pressure 135/40.

Examination of the blood revealed a hemoglobin of 88 per cent and a white-cell count of 6450 with 82 per cent neutrophils, 9 per cent lymphocytes and 10 per cent monocytes. The blood Hinton reaction was negative. The blood nonprotein nitrogen was 50 mg. per 100 cc. on entry and later normal. Examination of the urine was negative. An electrocardiogram showed sinoauricular tachycardia, incomplete auriculoventricular block and a further alteration of T waves — all consistent with a diagnosis of active myocardial involvement. Blood cultures were sterile.

tion rate was 0.8 mm. per minute. Tests for heterophil antibodies were negative at that time and on two subsequent occasions.

On the 12th hospital day the patient began to have a sensation of tingling like "pins and needles" in the feet and hands and a numbness of the trunk. When the toes touched the foot of the bed they felt as if charged with electricity. On the 14th hospital day he became slightly jaundiced. At that time, the icteric index was 25, the cephalin flocculation test ++++ and the prothrombin time 60 per cent. In succeeding days the paresthesias continued and profound muscle weakness appeared. The neurologic consultant noted mental confusion. A peripheral type of facial weakness on the right and a flaccid weakness of all four extremities with the



legs affected more than the arms, loss of tendon reflexes, but active abdominal and flexor plantar reflexes, exquisite muscle tenderness and impairment of all forms of sensation in the distal parts of the lower extremities. On the night of the 16th hospital day, the patient had a "nightmare" and was incontinent of urine. The icteric index was 10, the carbon dioxide combining power was 39 milliequiv per liter, and the blood sugar 123 and the blood nonprotein nitrogen 63 mg per 100 cc. The white-cell count was 35,100, with 59 per cent adult neutrophils and 16.5 per cent band forms, 0.5 per cent basophils, 7.5 per cent small lymphocytes, 2.5 per cent atypical lymphocytes, 1.5 per cent large lymphocytes, 4.5 per cent young lymphocytes, 4.0 per cent monocytes, 1.5 per cent young monocytes, 2.0 per cent young plasma cells and 0.5 per cent metamyelocytes. The cerebrospinal-

the anterior one was calcified. The chordae tendineae were shortened and thickened, as were the papillary muscles. The capacity of the left ventricle was twice normal, and the left ventricular wall was symmetrically hypertrophied. The endocardium was smooth except for an area of roughening and calcification, 2.5 cm in diameter, beneath the aortic valve. The cusps of the aortic valve were thickened and partially calcified, and their free edges were rolled and shortened. There was slight widening of the commissures between the right and left posterior cusps. The coronary ostia and arteries were patent. In the first portion of the aorta, for a distance of about 3.5 cm, the intima was uneven and discolored. Elsewhere in the aorta subintimal streaks of atheroma were visible. The tricuspid valve measured 11.5 cm, the pulmonary valve 7.7 cm, the mitral valve 10.2 cm and the

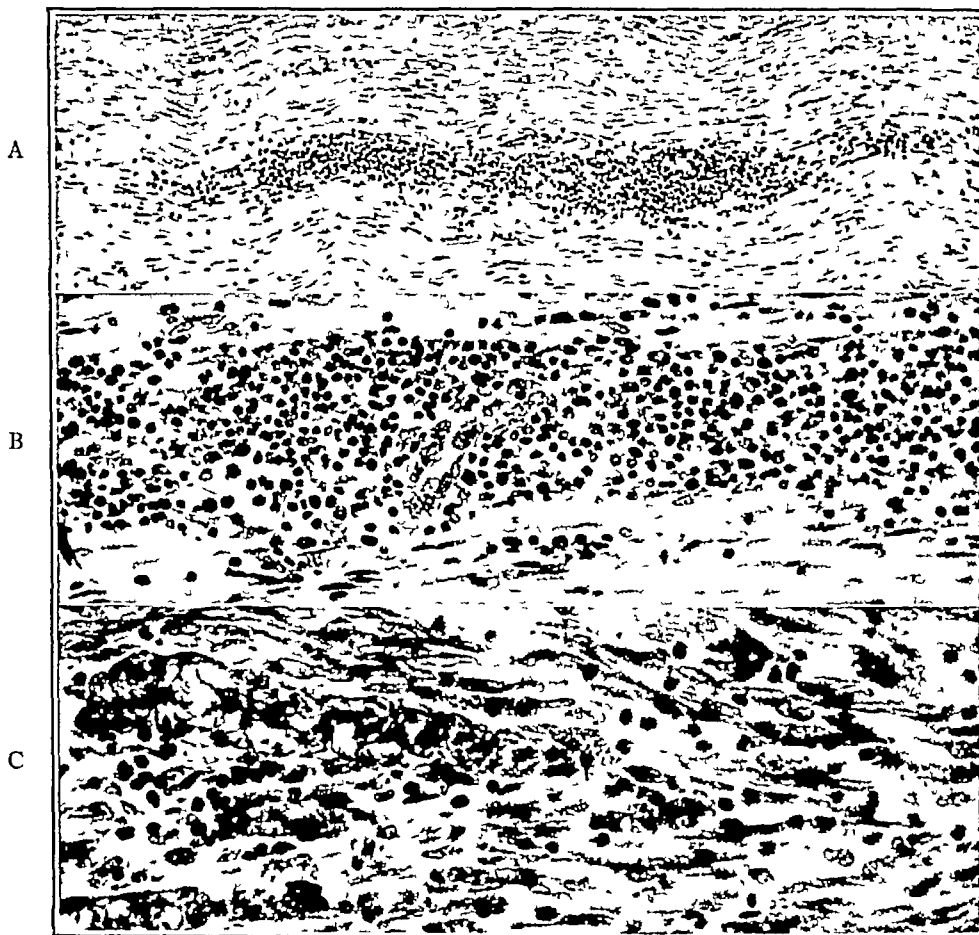


FIGURE 2 A Shows a Phloxine-Methylene Blue Stain of Peroneal Nerve, with Cellular Infiltration, and B a Higher Magnification of the Same Lesion to Demonstrate the Type of Infiltrating Cells. C Shows a Sudan III Stain of the Same Nerve (Note the Swollen, Vacuolated and Fragmented Myelinated Nerve Fibers)

fluid pressure was normal, the fluid was slightly yellow, it contained 20 mononuclear cells per cubic millimeter, the sugar was 54 mg, and the protein 112 mg per 100 cc, the Wassermann test was negative. Several brief, generalized convulsions occurred on the 17th hospital day, and during some of these the radial pulse disappeared. A few minutes after a convulsion respirations suddenly ceased at a time when the pulse was quite strong. Death occurred on the 17th day in the hospital.

**Autopsy** External examination of the body revealed nothing of note except for slight jaundice of the scleras and skin. The heart weighed 640 gm. The left auricle was dilated to about twice its normal capacity, the endocardium varied from pale to yellowish white and was calcified in two places. Both leaflets of the mitral valve were greatly thickened, and

aortic valve 7.7 cm in circumference, the right ventricle was 0.6 cm, and the left 1.7 cm in thickness.

The spleen weighed 580 gm. The surface was smooth and purplish gray. The cut surface was firm and purplish-red, and the malpighian corpuscles were well demarcated. The pulp was firm, and very little could be removed by scraping.

The liver weighed 1680 gm. The surface was smooth and reddish brown. The cut surface was firm, and the lobules were well demarcated by pink periportal tissue. The central veins could not be seen. The gall bladder and bile ducts were normal.

There was a generalized lymph-node enlargement. The nodes in the mesentery averaged about 2.0 cm in diameter. The largest mediastinal lymph node measured 2.5 by 2 by 1 cm, and the periaortic nodes were 4 by 4 by 1 cm. One lymph node adjacent to the common bile duct measured

4 by 2 by 1 cm but did not obstruct the flow of bile. There were five discrete lymph nodes along the hepatic duct. The axillary and inguinal nodes averaged 1.0 by 0.4 by 0.4 cm. The cut surface of all these nodes was firm, homogeneous and pinkish white.

The brain weighed 1380 gm. The leptomeninges of the brain and spinal cord were thin and transparent. There were no gross abnormalities of the brain, spinal cord or peripheral nerves.

Microscopical examination disclosed that there was an infiltration of plasma cells, lymphocytes, a few polymorpho-

The upper and lower lobes of the right lung and the upper lobe of the left lung revealed an interstitial infiltration of a moderate number of plasma cells, some lymphocytes and immature mononuclear cells of an undetermined type. The alveoli of these lobes were free from exudate except for the presence of a few 'heart failure' cells in some alveoli. The alveoli of the left lower lobe contained numerous polymorphonuclear leukocytes, some large mononuclear cells, many of which contained phagocytosed cells, and occasional immature mononuclear cells with a basophilic cytoplasm, type of cell undetermined. The alveolar capillaries contained



FIGURE 3. A Illustrates a Phloxine-Methylene Blue Stain of the Spinal Leptomeninges, Showing Cellular Infiltration. B a Cajal Silver Stain of a Spinal Ganglion (One Nerve Cell is Shrunken and Pyknotic and the Other Two are Disintegrated) and C a Sudan II Stain of a Spinal Ganglion to Show Cellular Infiltration and Nerve Cell Degeneration.

nuclear leukocytes and some large mononuclear cells both around and within the nerves of the epicardium. A few cells of the same types were scattered through the fat tissue. The myocardium showed a patchy interstitial infiltration of similar types of cells with more polymorphonuclear leukocytes present than in the epicardium. In addition there were occasional perivascular lesions consistent with Aschoff bodies. The endocardium contained a focal infiltration of cells of the same types seen in the myocardium and epicardium.

Both the mitral and aortic valves showed a marked increase in collagen and vascularization.

polymorphonuclear leukocytes, some plasma cells, some immature mononuclears as described above, and mast cells. The bronchioles contained an exudate similar to that in the alveoli. The alveolar walls were thickened and congested, and some showed swelling of the alveolar lining cells. The arterioles revealed hyperplastic changes, and an occasional one a necrotizing process. In a large artery there were sub-endothelial lipid cells and an infiltration of plasma cells and immature mononuclear cells. Stains for bacteria showed positive diplococci in the polymorphonuclear leukocytes, alveolar and bronchiolar exudates.

The submucosa of the trachea was infiltrated with plasma cells

Some of the malpighian corpuscles of the spleen were small and inactive Others had been replaced by plasma cells, histiocytes and occasional giant cells of the Langhans type The endothelium of the central arterioles in such follicles was swollen The pulp was congested and contained numerous plasma cells and polymorphonuclear leukocytes

The ganglions and the nerves of the stomach were infiltrated with cells as described elsewhere The muscularis showed an interstitial infiltration

There was an interstitial infiltration of some plasma cells, lymphocytes, large mononuclear cells and a rare eosinophil

There was a focal infiltration of plasma cells, lymphocytes and a rare eosinophil in the interstitial tissue of the kidneys (Fig 1B) A stain for fat showed none to be present

Sections from the lymph nodes from various regions showed essentially the same picture Their structure was well preserved The germinal centers were inconspicuous and inactive The sinuses contained large mononuclear cells, some of which had phagocytosed red cells In the sinuses there were also a few immature cells The surrounding connective tissue was infiltrated with plasma cells and lymphocytes

In sections from the bone marrow the granulocytic series were numerous, with normal maturation An unusual number of eosinophilic myelocytes were present Cells of the red-cell



FIGURE 4 A Demonstrates a Cresyl Violet Stain of the Lumbar Spinal Cord to Show Meningeal and Focal Infiltrations, and B a Higher Magnification Showing One of the Lesions in the Gray Matter (the Nodule Consists of Lymphocytes, Plasma and Mononuclear Cells Mixed with Microglial Cells and Astrocytes)

in the pancreas A small ganglion disclosed lesions similar to those described elsewhere

The liver cells in the centers of the lobules had disappeared, and in the spaces formerly occupied by them were plasma cells, polymorphonuclear leukocytes and large mononuclears, some of which contained pigment An occasional necrotic liver cell invaded by leukocytes was present A considerable number of bile capillaries were distended with bile The cells showed a moderate degree of fatty and hydropic eration The portal areas were infiltrated with numerous cells, polymorphonuclear leukocytes, occasional plasma cells and large mononuclear cells (Fig 1A)

series were markedly decreased in number The megakaryocytes were not remarkable In the sections from the vertebral and sternal marrow were several focal lesions made up of histiocytes and giant cells of the Langhans type

There was an interstitial infiltration of plasma cells and lymphocytes in the salivary gland

The pituitary body showed a perivascular infiltration of plasma cells, lymphocytes and large mononuclears in the posterior lobe

Sections of the peripheral nerves, dorsal and ventral lumbar roots, spinal ganglions, spinal cord, medulla, cerebellum, mid-brain, thalamus and cerebral cortex were stained

with cresyl violet. The nerves and ganglions were also stained with ORO for fat hematoxylin for myelin and silver for axon cylinders.

All the nerves, even the most peripheral twigs were infiltrated with large aggregates of lymphocytes and plasma cells, unidentified mononuclear cells and a few polymorphonuclear leukocytes. histiocytes were also increased in number. These cells were in the endoneurium, separating the nerve fibers and had also invaded the perineurium. The spinal sensory ganglion cells and sympathetic ganglions in the bowel and bladder were similarly affected. Most of the ganglion cells had disappeared and were replaced by clumps of satellite cells and phagocytes. Scattered nerve fibers had degenerated and round and oval shaped remnants of destroyed myelin remained. In only a few places had these myelin products been phagocytized by histiocytes. The majority of myelinated fibers were intact. The spinal roots were less involved than the nerves. The spinal and cerebral meninges contained infiltrations of lymphocytes, plasma cells and mononuclear cells and similar cells extended into the posterior horn via the entering root fibers. There were several clumps of microglial cells and lymphocytes and mononuclear elements in the white matter especially around blood vessels. Some of the anterior-horn cells were swollen and had undergone chromatinolysis. A few small blood vessels in the brain and spinal cord were surrounded by lymphocytes and plasma cells (Figs. 2, 3 and 4).

Cultures of the lungs, other organs and blood were not taken. Attempts to culture the lymph nodes and the spleen on chick embryos were unsuccessful, since the material was contaminated with an organism of the *Escherichia coli* group.

The anatomic diagnoses were acute infective polyneuritis, with extensive involvement of the peripheral nerves, spinal roots and sensory and sympathetic ganglions, acute interstitial myocarditis, hepatitis and nephritis, rheumatic heart disease, healed and active, stenosis and insufficiency of the mitral and aortic valves and bronchopneumonia of the left lower lobe.

In the following case the patient recovered after a few weeks, and hence the diagnosis was not verified pathologically, but the resemblance to Case 1 was so close that the clinical details are added to emphasize the greater frequency and non-fatal character of some cases.

**CASE 2\*** A 46-year-old man had been well until 3 weeks previously, when he became feverish and tired and voided dark brown urine. He improved after 3 or 4 days, returning to work, but malaise continued. Two weeks before admission he became nauseated and jaundice was noted, deepening during the next week, when numbness and tingling of the fingers and, soon afterward of the toes and feet set in. The paresthesias rapidly extended up the legs and were accompanied by muscular weakness of such severity that the patient could not stand or walk. There had been a 10-pound weight loss.

Notable items in the past history were rheumatic fever at the age of 17 years and the absence of exposure to a jaundiced person to metals, to transfusion or to inoculation.

Physical examination disclosed a mentally alert and co-operative patient. The skin was moderately jaundiced. There was a slight enlargement of all palpable lymph nodes. The heart was enlarged, the border of cardiac dullness extending 10 cm. to the left of the midsternal line, the second pulmonic sound was louder than the aortic, and a Grade III rasping systolic and a low pitched rumbling diastolic murmur were heard at the apex. The liver had an increased vertical diameter the lower edge being 5 or 6 cm. below the costal margin at the midclavicular line. The spleen was not palpable. There was no facial weakness or other disturbance of the cranial nerves. The muscles of the arms and legs were partially paralyzed. The legs were more affected than the arms and the proximal muscles slightly more than the distal ones. The muscles were tender and flaccid. All tendon reflexes, including the plantar, were absent, and the abdominal reflexes were retained. Vibratory and position senses were

reduced below the knees and in the hands. Touch sensation was questionably impaired and other forms of cutaneous sensation were preserved.

The temperature was 98 F, the pulse 88, and the respirations 20. The blood pressure was 120/60.

Examination of the blood revealed a hemoglobin of 105 per cent and a white-cell count of 12,400 with 83 per cent neutrophilic leukocytes, 8 per cent lymphocytes, 8 per cent monocytes and 1 per cent eosinophils. The nonprotein nitrogen and fasting blood sugar were normal. The cerebrospinal fluid was under normal pressure and except for a total protein of 80 mg per 100 cc. was normal. Tests for porphyrins (Watson method) were negative. Heterophil-antibody agglutinations were positive in a dilution of 1:64. The bilirubin was 3.85 mg per 100 cc. and the icteric index was ++++. The total blood protein was 7.7 gm per 100 cc. with 4.1 gm of albumin and 3.6 gm of globulin. The prothrombin time was 76 per cent. The urine contained urobilinogen in dilutions of 1:128 and gave a +++ test for bile but no albumin or cells were observed in the sediment. An electrocardiogram was normal.

During the last week in the hospital the degree of motor and sensory paralysis increased even though the jaundice lessened perceptibly. The patient became unable to lift his legs from the bed or to sit up without using his arms. All forms of sensation, including pain and touch, were impaired below the knees and elbows. Pain and burning paresthesias of the feet were experienced. The total protein in the cerebrospinal fluid rose to 143 mg per 100 cc. and there were 7 lymphocytes per cubic millimeter. The treatment consisted of bed rest, an ample intake of carbohydrate, protein and vitamins and intravenous aminoacids.

Throughout the following month the jaundice gradually disappeared, and strength and sensation slowly returned to the limbs. At the end of 3 months the patient had almost completely recovered. The only residual neurologic sign was absent ankle reflexes. The liver function was much improved, the cephalin-flocculation test was + and the icteric index 10. The last spinal fluid protein during the 8th week of the illness was still 68 mg per 100 cc.

The final diagnoses were acute infective polyneuritis, acute interstitial hepatitis and rheumatic heart disease with cardiac enlargement, mitral stenosis and regurgitation compensated (Grade I).

## DISCUSSION

Case 1 presented several puzzling features. With the development of "sore throat" and the abnormal lymphocytes in the circulating blood a diagnosis of acute infectious mononucleosis was entertained. However, the repeatedly negative tests for heterophil antibodies failed to substantiate this possibility. Then, when jaundice appeared and reduced liver function was demonstrated, the obvious diagnosis was acute infectious hepatitis, which would also have explained the abnormal lymphocytes in the blood smear. When, however, neurologic symptoms became manifest, the diagnosis was again unsettled. We knew of examples of both infectious mononucleosis and infectious hepatitis that were complicated by involvement of the nervous system but could not recall a case of an acute symmetrical polyneuritis associated with either of these diseases.

Post-mortem examination clarified some but not all of the peculiar clinical findings. The generalized weakness, dyspnea and dependent edema, the flatulence and abdominal distress and the albuminuria and slightly elevated nonprotein nitrogen were due to healed rheumatic heart disease and congestive heart failure. The finding of Aschoff bodies in the myocardium provided an explanation

\*This patient was observed in one of the medical wards of the Boston City Hospital while the report on Case 1 was being prepared.

for the abnormalities in the electrocardiogram. The upper abdominal pain could hardly have been caused by congestion of the liver, since it occurred when the heart disease was quite well compensated, a more likely possibility was enlargement of the abdominal lymph nodes or of the liver occurring in the terminal illness. The jaundice and impaired liver function were ascribed to the acute interstitial hepatitis or to a combination of hepatitis and central hemorrhagic necrosis. The atypical lymphocytes in the peripheral blood and the leukocytosis were probably part of an infectious disease that mobilized lymphocytes and other mononuclear cells for the extensive cellular infiltrations found in all the nerves and visceral organs. The paresthesias and sensory impairment and the ascending paralysis and reflex loss were manifestations of the acute polyneuritis. The cellular infiltrates in the spinal and cerebral leptomeninges and in the roots were the source of the cells in the cerebrospinal fluid. The convulsions may have been due to heart block (Adams-Stokes syndrome) or the leptomeningitis, and the foci of cellular infiltration in the brain and mental confusion may have had a similar basis. Death was due to the polyneuritis, which finally produced respiratory paralysis, the pneumonia being a contributing factor.

The pathological findings in this case were in general similar to those of the class of diseases called acute infective polyneuritis, the characteristics of which are widespread but uneven lymphocytic, plasma-cell and mononuclear infiltrations of the peripheral nerves, somatic and autonomic spinal ganglions and spinal nerve roots\*, irregular degeneration of myelinated peripheral-nerve fibers, varying degrees of change in the nerve cells of the spinal and autonomic ganglions, and swelling and central chromatolysis (axonal reaction) of the motor cells in the anterior and lateral horns of gray matter in the spinal cord. However, Case 1 differed in that the destruction of ganglion cells was much more extensive and the leptomeninges were infiltrated with lymphocytes, plasma and mononuclear cells—a reaction that occurs infrequently in acute infective polyneuritis. Despite these differences, some of which may be only quantitative, it seems to us that the most acceptable classification is in the group of diseases called acute infective polyneuritis. Whether the latter is a single pathologic entity or a pathologic reaction occurring in several different diseases has not been determined.

The histologic changes in the lymph nodes were not those described by Gall and Stout<sup>2</sup> in infectious mononucleosis. According to these authors, the most striking changes are seen in the germinal follicles and the extrafollicular lymphoid tissue.

\*Without cellular infiltrations, assuming of course that sufficient sections of the peripheral nerves, ganglions and roots are available for study, the pathological diagnosis must remain in doubt. It should be remembered that, on clinical grounds alone, polyneuritis due to toxic and metabolic disorders may closely resemble the acute infective variety.

The germinal centers are hyperplastic and contain immature cells, presumably stem cells, and histiocytes, many of which contain phagocytosed material. Mitotic figures are numerous. The extrafollicular lymphoid tissue, both cortical and medullary, contains large cells with basophilic cytoplasm. These cells they believe to be identical with the large mononuclear cells in the circulating blood, which are considered characteristic of infectious mononucleosis. Sections of the lymph nodes in Case 1 showed small, inactive follicles and none of the cells in the lymphoid tissue seen in infectious mononucleosis.

Nor were the lesions in the liver similar to those observed in the acute form of epidemic hepatitis described by Wood<sup>3</sup> and by Lucké and Mallory.<sup>4</sup> In acute epidemic hepatitis the destructive process is extensive, and usually all the liver cells are affected, although at times a narrow zone of liver cells persists at the periphery of the lobule. Furthermore, there are a proliferation of small bile ducts and an extensive cellular infiltration of the portal areas with large mononuclear cells, lymphocytes and plasma cells and some polymorphonuclear leukocytes and eosinophils. In Case 1 the liver showed a late stage of central necrosis, with the greater portion of each lobule unaffected, and there was no proliferation of the bile ducts. The cellular infiltrates in the portal areas were similar to those in acute epidemic hepatitis, but these are not characteristic of any one disease, such cellular infiltrations being seen in varied types of infection. The lack of hyperplasia and necrosis in the lymph nodes and spleen must be regarded as further evidence against epidemic hepatitis.

In short, then, autopsy in Case 1 showed lesions in the liver compatible with those in cardiac failure and an extensive interstitial cellular infiltration in practically every organ examined. The abnormal cells found in the blood stream were similar to the unidentified mononuclear cells seen in the visceral infiltrations. Their nature and histogenesis are obscure.

The association of visceral lesions in fatal cases of acute infective polyneuritis has been recognized by other workers. Lhermitte,<sup>5</sup> in 1929, and Lelong and Bernard,<sup>6</sup> in 1935, reported clinical cases in which acute polyneuritis was combined with icterus or subicterus. Bradford et al.,<sup>7</sup> McIntyre<sup>8</sup> and more recently Sabin and Aring<sup>9</sup> presented cases in which acute infective polyneuritis was accompanied by visceral lesions. These lesions consisted of infiltrations of lymphocytes, plasma cells and mononuclear cells in the liver, adrenal glands, kidneys and heart. Ours is the first case, however, in which there was both clinical and pathological evidence of visceral lesions.

Such a case raises interesting questions regarding the relation between acute infectious mononucleosis, acute infective polyneuritis and acute hepatitis.

Until the etiology of one or all of these diseases has been determined this matter cannot be definitely settled. It is our impression, however, that there are important clinical and pathological differences.

Unfortunately, no systematic attempt was made to culture a bacterium or virus in Case I. The pathological findings support the proposition submitted by Sabin and Aring that acute infective polyneuritis is a widespread systemic disease caused by a virus or bacterial toxin that involves the peripheral nervous system predominantly but may produce extensive visceral lesions of such severity as to become clinically manifest in exceptional cases.

### SUMMARY

An unusual case of acute infective polyneuritis with jaundice and atypical lymphocytes in the peripheral blood and pleocytosis in the cerebrospinal fluid is reported. The pathological changes consisted in lymphocytic, plasma and mononuclear-cell infiltrations of the peripheral nerves, ganglions and leptomeninges, widespread degeneration of the

larger nerve fibers in the peripheral nerves and spinal roots, destruction of the nerve cells in the spinal and sympathetic ganglions, and interstitial infiltration of the liver, kidneys, heart and other viscera with cells similar to those in the nerves.

A similar case in which the patient recovered and the diagnosis was therefore not verified pathologically, is presented.

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## EMPHYSEMATOUS GASTRITIS\*

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THE term "emphysematous gastritis" has been employed to designate an infection characterized by the presence of numerous small gas bubbles throughout the wall of the stomach. The lesion is closely allied to phlegmonous gastritis and to cystic pneumatosis, but has certain distinguishing features. Because this disease is so rare, an additional case report is presented below.

In the first case of this type, described by Fraenkel<sup>1</sup> in 1889, the patient died after several attacks of severe abdominal pain, bloody vomitus and diarrhea. Autopsy disclosed that the wall of the stomach was filled with masses of bacteria and small gas bubbles. Fraenkel named the disease "emphysematous gastritis"—a descriptive term that is not entirely satisfactory, since although it describes the presence of gas, it does not emphasize the element of infection.

A somewhat similar case was reported by Morton and Stubbs<sup>2</sup> in 1928. This patient also died, and *Bacillus welchii* (*Clostridium perfringens*) was identified as the causative agent.

In the most recent case, observed by Weens,<sup>3</sup> the patient swallowed several ounces of hydrochloric acid. Severe abdominal pain was followed by bloody vomitus. X-ray films of the stomach showed

characteristic gas bubbles throughout the wall. The emphysema gradually diminished, but extensive scar formation followed. The patient finally died of sepsis following a gastrostomy. At autopsy, a subdiaphragmatic abscess and multiple liver abscesses containing colon bacilli were found. Weens has summarized the literature, and has found no other cases of true emphysematous gastritis, although emphysematous infections of other viscera, such as the gall bladder, urinary bladder and uterus, have been recorded.

### DIAGNOSIS

The essential diagnostic features are severe abdominal pain, nausea and vomiting of blood, prostration, fever, leukocytosis and a typical x-ray picture. The course is usually progressively downhill with death from sepsis.

The disease must be differentiated from acute phlegmonous gastritis and cystic pneumatosis. Phlegmonous gastritis<sup>4</sup> is frequently ushered in by an alcoholic bout, or follows a chemical poison, such as hydrochloric acid, or trauma, such as esophagoscopy. The clinical course is much the same, but x-ray films do not reveal any intramural gas. The mortality is recorded as about 50 per cent.

Cystic pneumatosis is characterized by the presence of localized masses of gas-filled cysts in the wall of a viscus. It is uncommon in the stomach, although 175 cases of involvement of the small

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bowel have been collected by Jackson<sup>5</sup> The accumulations of gas are asymptomatic and are usually found to be incidental to other lesions at laparotomy If left alone, they tend to disappear spontaneously Baumann-Schenker<sup>6</sup> has reported the only case of cystic pneumatosis of the stomach that has been recognized by x-ray study before operation

Robbins<sup>7</sup> believes, from an x-ray point of view, that all cases in which intramural gas bubbles are demonstrated are variants of cystic pneumatosis It is our opinion, however, that cystic pneumatosis has only one feature in which it resembles emphysematous gastritis the presence of gas But in this respect also there is a variation, for the gas in the cystic pneumatosis is usually found in grape-like clusters of cysts, whereas in emphysematous gastritis, it is scattered throughout the walls of the stomach Emphysematous gastritis is much more closely related to and should be considered a special variant of phlegmonous gastritis

#### CASE REPORT

J. C. (M.G.H. 529108), a 15-year-old girl was admitted to the hospital at 8 a.m. on April 28, 1946, complaining of severe abdominal pain She had been entirely well until 36 hours before entry Soon after eating dinner, which included fresh salmon but nothing else unusual, she experienced epigastric



FIGURE 1 Scout Film of the Left Upper Quadrant of the Abdomen on the Sixth Day of the Disease

Multiple small gas bubbles are visible throughout the fundus of the stomach There is no free gas in the peritoneal cavity Fluid is present in the left pleural cavity

distress The remainder of the family, who had had the same meal, had no unusual symptoms During the night, epigastric cramps developed and were followed by nausea and vomiting Shortly after the first attack of vomiting, the bowels began to move and there were five loose movements in the following 12 hours After several episodes the vomiting ceased but the nausea continued The abdominal pain continued to increase in severity It remained in the epigastrium, finally radiating directly behind the sternum It became steady and then more intense A physician was called 18 hours before entry Paregoric was prescribed Four hours later the patient was seen by a surgical consultant, who found that the abdomen was soft throughout and not distended Peristalsis was normal It was believed that she had an acute gastroenteritis that would respond to rest

Four hours before entry, the pain became much more severe and was somewhat relieved by sitting up in a chair At that time, 8 mg. of morphine given intramuscularly had no effect upon the pain, the abdomen had become silent and more distended The patient looked definitely sicker than she had before and felt very ill

Physical examination showed a rather frail, extremely pale girl who was obviously very sick The skin was cool and

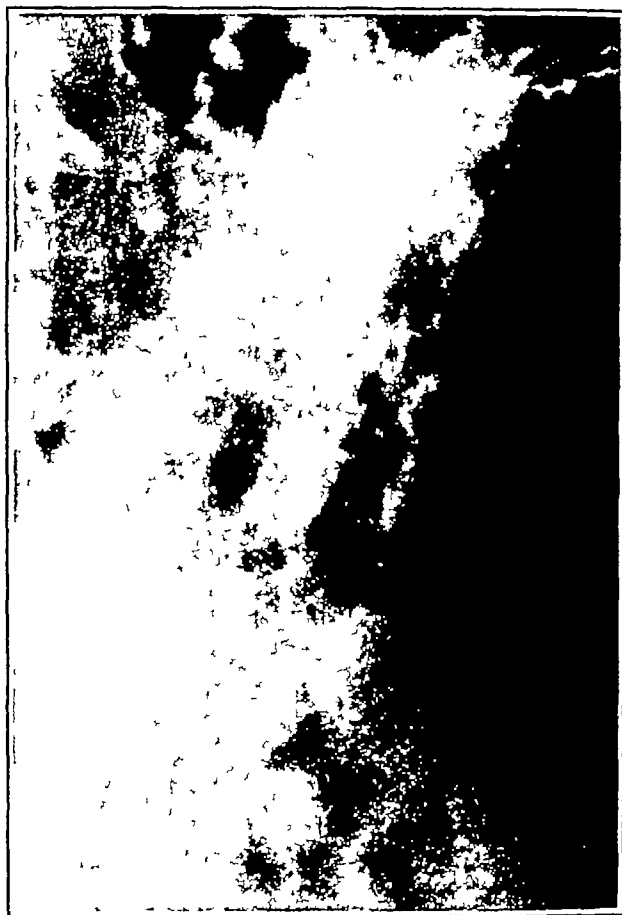


FIGURE 2 Roentgenogram on the Tenth Day, Showing Multiple Gas Bubbles in the Wall of the Body of the Stomach No areas of mucosal ulceration could be demonstrated

moist The heart and lungs were normal The abdomen was markedly distended, rigid, tender throughout and silent Rectal examination was negative

The temperature was 99.5°F by rectum, the pulse 125, and the respirations 25 The blood pressure was 72/26

Examination of the blood disclosed a white-cell count of 39,500, with 96 per cent neutrophils, 2 per cent lymphocytes and 2 per cent monocytes A urine specimen could not be obtained

A nasal tube was passed immediately, and to our great amazement a total of 2000 cc. of coffee-grounds liquid was obtained from the stomach This produced some improvement in the general condition The abdomen became softer and less tender The diagnosis of acute hemorrhagic gastroenteritis seemed the most tenable The patient was immediately given intravenous injections of dextrose in physiologic saline solution, with resulting improvement of the systolic blood pressure, which rose to approximately 100 Eight hours later, she was very toxic and disoriented Climbing out of bed, she pulled out the intravenous needle A few minutes thereafter she developed a severe state of shock, and when seen at that time, it appeared that death was imminent While blood transfusions were being prepared, 250 cc. of plasma was rapidly given This was followed by 850 cc. of whole blood At that time, the temperature was 104°F by

rectum the pulse 160 and the respirations 25. During the first 24 hours in the hospital the patient received a total of 3800 cc. of physiologic saline solution plasma and blood intravenously and maintained a urinary output of 600 cc.

On the following morning she was slightly improved. She was still very toxic and dehydrated with a silent distended abdomen that was slightly tender throughout. The drainage from the intubing Levin tube was still profuse and coffee ground in nature. She then began to run a septic type of temperature with a rise to 102 F. every evening and a pulse ranging up to 120. Two days after entry the gastric drainage had cleared considerably and for the first time showed a gross blood. A hemoglobin (photo) of the gastric content that were aspirated during that period was 4.6 gm. It was estimated that the amount of blood lost from hemorrhage was therefore at least 1000 cc. Three days after entry it was possible to start feeding by mouth. The abdomen was still somewhat distended but peristalsis had returned to normal. Examination of the chest at that time showed no evidence of fluid at the left base and some edema of the face had developed. Fluid in the chest gradually increased in amount. On the 7th day a chest tap was done. A total of 360 cc. of straw-colored slightly cloudy fluid was withdrawn after which 25 000 units of penicillin was inserted. The chest fluid showed no growth on culture.

At the time of entry an x-ray film had been taken of the abdomen. This was not remarkable except for the presence of several gas filled loops of small bowel. Six days after entry, repeat plates were made. At that time a most remarkable picture was observed. The stomach was seen to be dilated, containing a large quantity of gas. Surrounding the entire fundus of the stomach and extending well down on the antrum were numerous small gas bubbles which were found on all walls of the stomach, but no evidence of free gas in the peritoneal cavity could be found (Fig. 1). Fluid filled the lower two thirds of the left pleural cavity. The x-ray film superficially suggested a stomach full of masses of food, but we were certain that the stomach was empty of solids and fluid.

With the presence of an increasing amount of fluid in the left side of the chest and disappearance of the edema elsewhere it was believed that a subdiaphragmatic abscess was developing. The penicillin dosage was increased. Ten days after entry barium was given by mouth. By a barium meal the air bubbles throughout the fundus were shown to lie within the gastric wall (Fig. 2). No areas of ulceration could be demonstrated in the stomach and the duodenal cap and loop were normal. There was no evidence of subdiaphragmatic inflammatory change or massive pleural effusion. There was no movement of the left leaf of the diaphragm.

Within the following week the temperature gradually declined and the patient finally became afebrile about 2½ weeks after entry. Penicillin was discontinued 3 days later. Three weeks after entry x-ray examination showed the swallowing function to be normal. No disease was noted in the esophagus, stomach or duodenum. The fundal portion of the stomach was displaced downward from the left leaf of the diaphragm, probably owing to inflammatory changes taking place in that region. The left leaf of the diaphragm showed marked limitation of motion. The fluid in the chest had disappeared. Meanwhile, the white-cell count had gradually declined to normal, and the hemoglobin was maintained at 12 gm.

Specific therapy consisted chiefly of penicillin of which 192,000 units was given intramuscularly daily for the first 5 days. This dosage was then increased so that approximately 300,000 units was administered daily. Sulfadiazine was given intravenously at entry. A maximum blood level of 4.2 mg. per 100 cc. was obtained. The sulfadiazine was discontinued after the initial dose because of the low urinary output and fear of renal complications. The patient also received large doses of adrenocortical extract during the period in which she was in shock. Large doses of vitamins K, C and B were given intravenously. She received a total of five blood transfusions. Unfortunately no Amigen was available at the time but the serum protein was maintained over a level of 5.5 gm. per 100 cc. during the hospital stay.

Culture of the gastric contents shortly after entry showed abundant *Escherichia coli*, a moderate number of non-hemolytic streptococci and a few colonies of *Staphylococcus aureus*. Stool cultures on the first available specimen showed no pathogenic organisms.

During the illness the weight had dropped from 85 to 67 pounds. A month after discharge the patient was entirely asymptomatic and had gained 8 pounds. Repeat x-ray films at that time showed no disease in the chest or stomach. A year later the patient reported that she was in perfect health and had had no further gastric symptoms.

## DISCUSSION

The cause of the disease in this patient is not clear. It is probable that she first had an acute gastroenteritis, accompanied by vomiting, which produced rupture of the gastric mucosa. This was followed by profuse bleeding and gastric dilatation and then by an invasive infection of the wall of the stomach with nonspecific organisms. It is possible that gas within the lumen of the stomach was actually forced into the stomach wall as well as through mucosal rents, although the wide distribution suggested the formation of gas bubbles by the invasive bacteria.

Although a mixture of *Esch. coli*, nonhemolytic streptococci and *Staph. aureus* was found in the gastric contents, the exact organisms that invaded the gastric wall were not known. Occasionally, mixed infections of *Esch. coli* and nonhemolytic streptococci will produce gas, thus, gas is observed in infections of the leg, or in subdiaphragmatic abscesses from which these organisms can be grown. It can therefore probably be assumed that this mixed infection was the source of the gas.

The extreme prostration was due primarily to blood loss and secondarily to infection. The blood loss, judging from the hemoglobin level of the gastric contents, was at least 1000 cc. After this blood had been replaced, the signs of sepsis became more apparent. The subdiaphragmatic inflammation gradually subsided without the formation of a definite abscess.

Recovery from infection, we believe, was due chiefly to the rather large doses of penicillin employed. The early administration probably maintained the sterility of the subdiaphragmatic and intrapleural fluid collection. Similarly, control of the intragastric infection prevented the development of late scar formation and gastric deformity.

## SUMMARY

To 3 cases of emphysematous gastritis collected from the literature a fourth is added. The other 3 patients died. The patient in the case presented above, after penicillin therapy, recovered without complications.

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## WHAT INDUSTRY THINKS ABOUT THE MASSACHUSETTS MEDICAL SOCIETY'S PROGRAM OF MEDICAL CARE FOR THE PEOPLE OF MASSACHUSETTS\*

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**G**RANTING that it is necessary to provide more adequate medical care for our citizens, the question arises, How shall this care be distributed? How shall it be administered, and how shall it be financed? Naturally, the further question also immediately arises, What part should the United States Government have in this program? At the present time several bills regarding medical care are pending before Congress. The most important of them are the Wagner-Murray-Dingell Bill (S 1606), the Maternity and Child Welfare Act of 1945 (S 1318) and the Taft Bill (S 545).

The basic principles of medical care as presented by the Society list two main questions. The first is the provision of adequate medical care for those who cannot afford it. The second is the furnishing of that care for those who can afford it. Very properly, I think, the first principle listed is that medical care by voluntary prepayment plans or by direct payment is the responsibility of the local or state government. Part of the burden of this responsibility may be assumed by charitable agencies, such as the various community funds, and part of it by federal grants to state programs, to be administered by state boards of health. This, I think, is one of the fundamental principles of any medical-care program—that it be administered by the government that is closest to the people—that is, by the state or local government. Because the federal Government has at the present time taken over so many of the fields of taxation it seems essential that the financial aid should come from the federal Government. Its administration, however, should be handled on the local level.

The second principle is correctly stated as medical care of those who are able to purchase it by voluntary prepayment plans or by direct payment, which is the responsibility of the individual. In this field government participation should be purely supplementary and educational, and probably any government assistance in a financial way should be along those lines.

The basic principles also state that the eligibility for receiving benefits aided by federal grants should be determined by the individual states, that in any event the patient should have the free choice of his physician, group of physicians, clinic or hospital from among those participating in any plan, government or voluntary, and that on the

other hand the physician, group of physicians, clinic or hospital should have the right to refuse or accept the patient and the individual physician should be free to elect or reject without prejudice his individual participation in any medical-care plan, furthermore, physicians, hospitals and nurses should receive adequate remuneration for their services. These principles are essential if citizens are to have the freedom of choice and the recognition of individual rights that are an inherent part of the system of free enterprise. Industry is strongly opposed to any form of socialized medicine, which is merely one step farther toward actual socialism, and the Wagner-Murray-Dingell Bill, especially Title 2 of this act, is no more or less than compulsory health insurance. Industry is very wary of any compulsory government programs, having been burnt by a good many during the last few years.

The Society's principles are carried out in great part by the prepayment hospital plan, the Blue Cross, which is said to act for about 50 per cent of hospital admissions and after ten years of experience has come to be an accepted and important part of the medical program of the Commonwealth. The Blue Shield, which covers surgical and obstetric care rendered in the hospital for approximately 600,000 persons in the Commonwealth and which soon will cover all medical hospital care and surgical and medical services rendered outside the hospital, very ably complements the Blue Cross.

The third operating program of medical care, that of the United States Veterans Administration, covers approximately 600,000 Massachusetts veterans through all types of medical care. Thus, a large proportion of the five million people in the Commonwealth participate in one or more of these three plans.

From the point of view of industry, the Workmen's Compensation Act provides not only hospital, surgical and medical care for all persons injured in industry or in any commercial enterprise or those who are suffering from an occupational disease incurred in the course of their employment but also certain cash benefits for specific injuries and a weekly payment with a maximum of \$25 in addition to \$2.50 for each dependent during total incapacity and additional weekly payments during partial incapacity. This program covers approximately one fourth of the population and cost industry in 1946 about thirty million dollars. The gap in medical care for persons engaged in industry concerns those who are unable to work because of

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sickness and accidents occurring outside the course of the worker's employment. Through the assistance of the Blue Cross, the Blue Shield and the Veterans Administration, as well as by voluntary sickness and accident plans set up by various industries, this gap is rapidly closing. In 1944 the Advisory Council of the Employment Security Division conducted a survey under the authority of the General Court and found that in establishments employing 20 or more persons, 65.9 per cent were covered by some form of nonoccupational sickness or accident protection.

In 1946 a further investigation by the same agency showed that in establishments employing 20 or more persons, such coverage had increased to 71 per cent, and establishments of less than 20 employees, then surveyed for the first time, disclosed that nearly 64 per cent of the workers had some degree of protection against wage losses due to illness. Thus, this gap is rapidly being closed through entirely voluntary plans.

The demand has arisen in the same quarters as the demand for socialized medicine that a cash sickness-benefit plan be made compulsory for industry. Rhode Island now has such a plan based on the employment security or state fund system. California has a plan financed through a state fund, to which contributions are made as set by law or through private plans under state supervision. New Jersey is considering a proposal, which to date has not become law, for a cash sickness-benefit plan for industry, to be financed by private operation under state supervision. After a careful study of these systems, the Advisory Council recommended that if such a system were instituted it be a privately operated plan under state supervision with the establishment of minimum standards that would preserve the present plans in operation throughout the state. This, I think, is absolutely essential if such a plan is to be put into effect. Industry, however, is not yet ready to accept a compulsory cash sickness-benefit plan. The Ad-

visory Council in its first report to the General Court in 1945 stated as follows:

the role of government should be one of added impetus to the establishment and expansion of private plans rather than in direct participation. The remarkable growth of group insurance, Blue Cross hospitalization and prepaid medical care, in addition to the long-established individual health and accident insurance policies, is evidence that in Massachusetts private enterprise is meeting the problem and will continue to assume its responsibility if permitted to do so.

This, I believe, is still the point of view of industry, and I think that it coincides with the basic principles expressed by the Massachusetts Medical Society.

In conclusion, the two principles clearly set forth, which must govern all attempts to provide further medical care for the people of Massachusetts, are that the local or state government should assume the responsibility of providing adequate medical care for those unable to obtain it (a great part of this burden should be furnished by federal grants, but the administration should be purely on the state level) and that medical care for those who are able to purchase it by direct payment, voluntary prepayment plans or payroll deductions is the responsibility of the individual. This may be met through collective-bargaining agreements with his employer if he is employed, through voluntary agreements entered into between employer and employee, through private insurance sickness and accident coverage, through the Blue Cross and the Blue Shield and through benefits granted because of the applicant's status as a veteran. Before any compulsory plans are instituted along these lines, the voluntary plans listed above should have a chance to expand and to meet the responsibility. Furthermore, any plan, whether governmental or voluntary, must contain certain safeguards so that there will be absolute freedom of choice between patient, physician and hospital, and adequate remuneration for those whose services are given under such plans.

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**Correction** On Page 772, in the fourth line of the last paragraph of the summary of the paper "Syphilitic Primary Atrophy" by Drs. Levin, Trevett and Greenblatt, which appeared in the November 20 issue of the *Journal*, "artificial fever" should be changed to read "fever therapy."

## MEDICAL PROGRESS

### THE NASAL CARRIER OF BETA-HEMOLYTIC STREPTOCOCCI\*

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IN spite of the large number of accumulated data concerning the beta-hemolytic streptococcus and its effect on the human host, we are still largely unable to control its endemic reservoir and potential epidemic spread. As a result of the tragic mortality following the influenza pandemic of 1918, intensive efforts were carried out during World War II, first in Great Britain and later in this country, to devise means of curbing the spread of hemolytic streptococci and other respiratory infections, particularly among military recruits. These studies approached the problem from many angles, including chemotherapeutic,<sup>1, 2</sup> immunologic<sup>3</sup> and environmental means of control.<sup>4</sup> In spite of accurate methods of typing hemolytic streptococci,<sup>5</sup> the brilliant development of a new and potent therapeutic agent such as penicillin and the advances made in the understanding of the importance of dust and air in the transport of respiratory disease,<sup>6-11</sup> no single widely applicable and effective control method was devised on either side of the Atlantic to prevent the spread of epidemic streptococcal pharyngitis and tonsillitis and their unfortunate sequelae.<sup>12-14</sup>

With this recent experience in mind, it seems that the classic public-health measures of detection and isolation or treatment of the source of epidemic infection may in the future have to be invoked more often in training camps, schools and institutionalized populations when streptococcal infection approaches dangerous levels. It is well known that the rate of streptococcal pharyngeal carriers may rise from the normal 5 to 10 per cent to a level of 50 to 60 per cent during the development of an epidemic, and until recently there was no unanimity of opinion concerning the relation of a rising carrier rate to the pathogenesis of an epidemic, frequently, clinical streptococcal disease did not parallel the carrier rate,<sup>15, 16</sup> nor was there always a rise in the pharyngeal carrier rate to serve as a sign of an approaching epidemic.<sup>17</sup> Since mass sulfadiazine prophylaxis failed, owing to the appearance of sulfonamide-resistant strains,<sup>18, 19</sup> control of all the carriers has not been feasible by any method devised to date.

Hamburger and his associates<sup>20</sup> have recently proved the existence of the "dangerous" nasal car-

rier of beta-hemolytic streptococci, who disseminates at least one hundred times the numbers of organisms from his respiratory tract as patients or carriers with pharyngeal implantation only. The possibility of identifying and controlling the relatively few such carriers offers a new method of preventing streptococcal epidemics and solves many discrepancies in the epidemiologic pattern of streptococcal disease. It is the purpose of this paper to assess the evidence that the nasal carrier transmits the bulk of streptococcal infections of the respiratory tract and to review all the known factors pertaining to this condition.

#### METHODS USED

Recognition of the importance of nasal carriers occurred more or less as a by-product of quantitative studies of environmental contamination by the Commission on Air Borne Infection under the direction of Dr O H Robertson. In these studies extensive use was made of the conveniently identified and typed hemolytic streptococcus as an indicator organism of respiratory contagion in Army hospital wards and barracks, in the course of studies on the control of air-borne and dust-borne contagion. A number of methods were employed in these studies, many of which, although simple, reflect the efforts made to quantitate the amount of environmental contamination by patients and carriers.

The daily streptococcal output of ward patients was estimated, sterile cloth patches 12.7 by 12.7 cm being stapled overnight to the bottom sheet of the patient's bed. These were subsequently subcultured by rinsing in broth and plating aliquots, from which counts could be made.<sup>20</sup> Previous studies had demonstrated that the bottom sheet showed the highest degree of streptococcal contamination of any item of the bedding.<sup>21</sup>

The potential nasal streptococcal output of patients and carriers was estimated by means of the standard nose-blow test, in which, after sterilization of the hands, the nose was blown three times into a sterile handkerchief, 12.7 by 12.7 cm in diameter, which was subsequently subcultured as described above.<sup>22</sup>

The number of streptococci residing on the hands was estimated both before sterilization and after the nose-blow test, by washing of the hands for a constant interval in a standard amount of broth, from which cultures were obtained.<sup>22</sup>

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Cultures were made of clothing, bedding and floor dust, the suction device described by Lemon<sup>22</sup> being used. The entire exposed upper surface of the blankets as made up on the bed was "vacuumized" for a constant interval, and subcultures were made of the dirt trapped in the scrubbing chamber of the device. The outer surfaces of blouses, shirts, trousers and coats were similarly cultured, and measured areas of floor surface underneath or around carriers' beds could be sampled with the same device.

Air cultures utilizing both settling plates and the suction device previously described, as adapted for collection of air-borne bacteria, were made.<sup>23</sup> The suction device has a known efficiency for collection of air-suspended bacteria and virus close to 90 per cent and can sample fairly large volumes of air, from 10 to 30 cubic feet. Pour plates made from the scrubbing fluid in the sampler in suitable dilution can be studied for both total bacteria and air-borne hemolytic streptococci.

Cultures of the pharynx bilaterally in the region between the anterior and posterior tonsillar pillars were made at daily, weekly or monthly intervals as indicated. At the same time nasal cultures were obtained by the use of slightly thinner swabs rubbed over the mucosa of the anterior nares to a depth of not more than 2.5 to 3.0 cm.

All streptococcal cultures from the environment were poured in duplicate blood-agar gentian violet (in a 1,500,000 to 1,750,000 dilution) plates for counting and subsequent grouping and typing by the methods of Swift, Wilson and Lancefield.<sup>8</sup> Nose and throat cultures on plain blood agar were carefully described, and the amounts of streptococcal growth roughly estimated, prior to grouping and typing.

A limited number of carriers and healthy controls were studied for anti-streptolysin "O" titer variations, the method as modified by Rantz and Randall<sup>14</sup> being utilized.

The investigations were carried out over a period of four years (1942-1946), chiefly at Chanute Field, Illinois, Camp Carson, Colorado, Fort Lewis, Washington, and the University of Chicago School of Medicine. The co-operation of the United States Army Medical Department facilities at these posts was of great help, and the work was part of an extensive program of research administered by the Army Epidemiological Board, Preventive Medicine Division, Office of the Surgeon General.

#### EPIDEMIOLOGY AND CHARACTERISTICS OF THE NASAL CARRIER

Early in the course of these investigations certain basic facts became evident that later led to the nasal carrier studies. Parallel studies in hospital wards and Army barracks early in the war indicated that the rate of bacteriologic and clinical cross infection with a given type of streptococcus could usually be correlated with the predominance of this type

in the air or dust from floor and bedclothes.<sup>24, 25</sup> Furthermore, analysis of the rate of air and dust contamination in different portions of a hospital ward or barracks squad room revealed definite foci from which the predominant streptococcal type originated. These marked variations in the degree and type of environmental contamination, however, could not always be related to the numbers of streptococci in the pharynx and saliva of the personnel present. Some patients with clinical pharyngitis and strongly positive throat cultures were obviously rapidly seeding their environment with streptococci, whereas many others equally sick distributed very few streptococci to their bedding, clothing or surroundings. The bedding of ambulatory pharyngeal carriers in the barracks was frequently no more highly contaminated by streptococci than that from beds of noncarriers, and in many cases there was no similarity of types, indicating that these beds had been seeded from some other source.

Eventually, a patient with clinical sinus disease was observed by Hamburger to be a most profuse disperser of streptococci, and routine nasal cultures were then instituted. These soon disclosed that almost all cases or carriers of streptococci with strongly positive nose cultures could be classified as "dangerous" in that they were seeding their environment with tremendous numbers of micro-organisms each day, as measured by any one of the several tests employed. Carriers or patients in whom the nasal cultures were weakly positive usually showed less ability to disseminate streptococci, although they often exceeded the simple pharyngeal carriers in this respect.<sup>26</sup>

Since the phenomenon of dosage is of such importance in the determination of experimental infection, and since the degree of dust and air contamination must reflect the quantitative fluctuations in the sum total of streptococcal excretion by carriers and cases, it is of interest to review the differences in the numbers of hemolytic streptococci dispersed by the nasal carrier in contrast to the simple pharyngeal carrier.

Nasal carriers who were "strongly positive" were found to be capable of blowing out an average of 11,000,000 streptococci by the nose-blow test. At times as many as 1,000,000,000 organisms were expelled, and it should be emphasized that some of these patients showed minimal evidence of coryza or rhinitis. Very few if any streptococci were ever found in the nose blows of pharyngeal carriers with negative nose cultures, and weakly positive nasal carriers gave intermediate results. During induced sneezing and coughing, nasal carriers were found to excrete a significantly larger number of streptococci than the pharyngeal carriers, although no significant differences were found in the salivary content of these bacteria.<sup>27</sup>

The hand washes of 74 pharyngeal patient carriers yielded an average of only 4700 streptococci per test,

whereas 106 nasal patient carriers yielded an average of 790,000 organisms. As might have been expected, sterilization of the hands of these nasal carriers by washing in soap and water followed by a rinse in 70 per cent alcohol was considerably more difficult than that of the pharyngeal carriers. The hands of

figures, no significant differences were observed between cases with and without a scarlatiniform rash.<sup>20</sup>

Somewhat less marked differences in the blanket content of streptococci were noted in the barracks surveys of beds of ambulatory nose and throat carriers. Both strongly and weakly positive nasal carriers were included in the statistics, and the latter were shown to cause much less contamination of the bedding.<sup>21</sup> Also, no doubt many beds showed evidences of the prolonged survival of streptococci in blankets belonging to men who had once been both pharyngeal and nasal carriers but in whom the nose culture had cleared by the time of the survey. Streptococci have been shown to survive in bedding for periods as long as 5 months.<sup>27</sup> In the barracks,

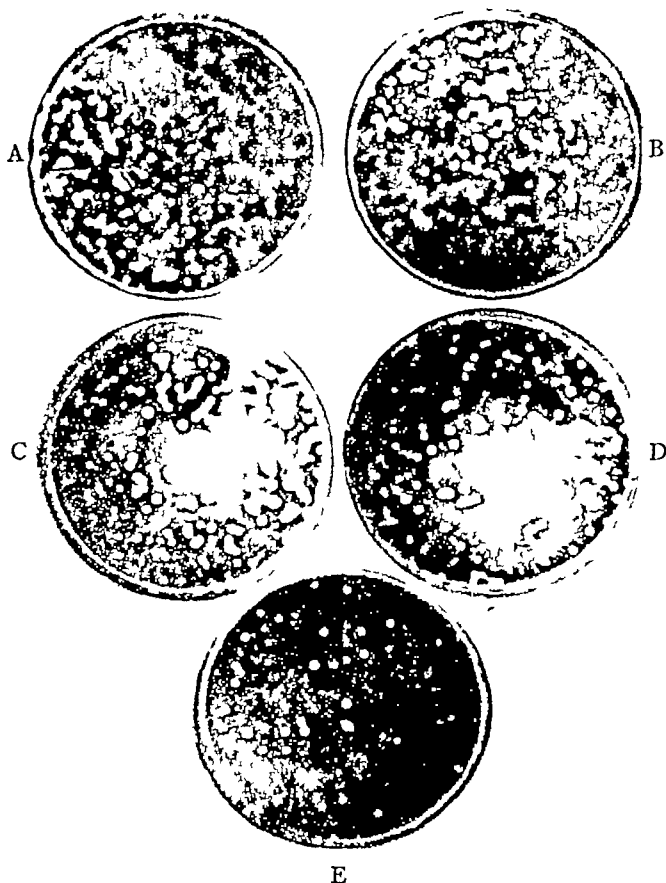


FIGURE 1 *Environmental Cultures, Using a Bubbler-Suction Sampler, from the Vicinity of an Asymptomatic Ambulatory Nasal Carrier (Nose and Throat Cultures Strongly Positive)*

A demonstrates culture of blankets on bed (75,800 streptococci), B culture of comforter (62,100 streptococci), C culture of blouse (20,200 streptococci), D culture of shirt (17,800 streptococci), and E culture of floor dust immediately surrounding and beneath bed (6700 streptococci). The figures represent only a small percentage of the total organisms present, successive samplings yield almost as many streptococci as initial tests. Plates usually represented 1/100 of the total culture.

nasal carriers were resoiled back to their original state by a few nose blows into a sterile handkerchief. Forty per cent of the pharyngeal carriers were noted to have negative hand cultures.<sup>22</sup>

The accumulation of streptococci on the cloth patches exposed overnight on the beds of hospitalized patients occurred at a rate about one hundred times as fast in the nasal patient carriers as in the pharyngeal patient carriers. Patients with negative nose cultures usually yielded only 600 to 900 organisms by the patch test, whereas an average of 50,000–60,000 streptococci were recovered from tests on patients with strongly positive nasal cul-

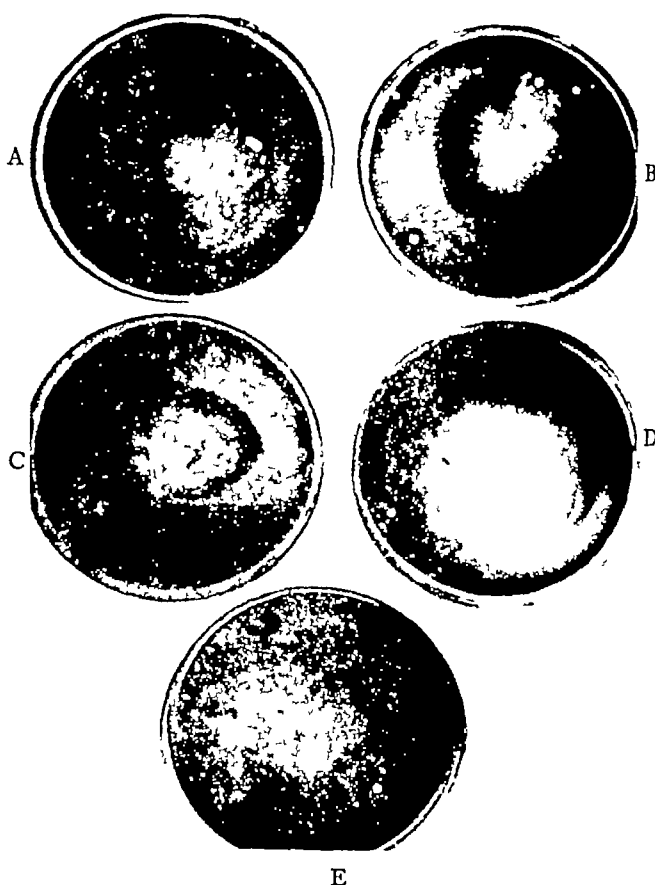


FIGURE 2 *Environmental Cultures, Using Same Technic as That in Figure 1, from the Vicinity of an Asymptomatic Ambulatory Pharyngeal Carrier (Nose Cultures Negative, and Throat Cultures Strongly Positive)*

A demonstrates culture of blankets on bed (900 streptococci), B culture of comforter (500 streptococci), C culture of blouse (negative), D culture of overcoat (100 streptococci), and E culture of floor dust immediately surrounding and beneath bed (100 streptococci).

the beds of nasal carriers yielded an average of 66 per cent more streptococci than those of pharyngeal carriers, furthermore, the same type was recovered from nasal carriers and bedding in 74 per cent of cases, as contrasted to only 30 per cent of pharyngeal carriers. The streptococcal content of bedding

belonging to both types of carriers was significantly greater when the same type was recovered from carrier and bed, as might have been expected.

Further studies of the environment of individual nasal and pharyngeal carriers in barracks, in whom the approximate duration of the carrier state was known, demonstrated again the hundredfold difference in amount of streptococcal dissemination to the environment (Fig 1 and 2), and in several cases the nasal carriers were observed to initiate a localized barracks epidemic caused by their own type of streptococcus.<sup>27-29</sup> It was also found that if the nasal carrier state persisted for four to six weeks, these dispersers could continue to be distinct hazards to their barracks mates, especially if they were transferred to another barracks whose personnel had not been previously exposed to their strain.

The numbers of air-borne streptococci were found to be directly dependent on the presence or absence of nasal carriers of beta-hemolytic streptococci, both in hospital wards and in Army barracks. Over twenty-five times as many streptococci were recovered from the air of a ward housing patients with strongly positive nasal cultures as from the air of a similar ward housing tonsillitis-pharyngitis patients with positive pharyngeal cultures only.<sup>30</sup> In the barracks, whenever large numbers of hemolytic streptococci were recovered from the air (up to 100 to 150 per cubic foot), a nasal disperser of streptococci was identified in the personnel.<sup>31</sup>

The majority of traceable hospital cross infections were found by Hamburger to be due to nasal carriers on the wards. Almost all patients who spread infection had high streptococcal outputs as measured by the patch test (from 40,000 to 500,000 organisms) whereas the majority of patients who failed to spread infection had less than 40,000 streptococci on the most highly contaminated patch. Eleven of 12 cases of ward cross infection were traced to nasal carriers, and only 1 to a pharyngeal carrier. A food-borne streptococcal epidemic was traced to a food handler with a strongly positive nasal culture who handled pies in the incubation period of the pharyngitis, cultures of the hands yielded 10,000,000 organisms of the type responsible for the epidemic.<sup>32</sup> As mentioned above, barracks epidemics were traced to single nasal dispersers among the personnel. One asymptomatic nasal carrier caused 10 cases to be admitted to the hospital from his barracks in two weeks. He was hospitalized for another three weeks for study of the streptococcal output and treated for five days with full doses of sulfadiazine, during his hospital stay he acquired another streptococcal type and was still carrying large numbers of streptococci in his nose on discharge. The new type was not present in any of the personnel of the new barracks to which he was assigned, within a few days he had heavily contaminated the bedding, floor dust and air of both floors of this barracks, and induced an epidemic of

streptococcal cross infection involving 30 per cent of the personnel. Four patients who carried the new type of streptococcus were admitted to the hospital from this barracks during the next two-week period. Extensive environmental contamination was found to precede the appearance of cross infections.<sup>29</sup> This patient illustrates the fallacy of present-day quarantine regulations and the role that the hospital itself may play in the dissemination of streptococcal disease among the population it serves.

Finally, the nasal carrier rate of troops was found to correlate well with the rates for streptococcal disease. In units having a low incidence of streptococcal disease (0.4 per cent of personnel hospitalized in a six-week period) the nasal carrier rate was 0.13 per cent, or 1 for every 41 pharyngeal carriers. Units having a moderately high incidence of streptococcal disease (5.7 per cent of personnel hospitalized) showed a nasal carrier rate of 4.2 per cent, or about 1 nasal carrier out of every 4 throat carriers. Under epidemic conditions in which nearly a third of a unit was hospitalized in this period, 40 per cent of the population were found to be nasal carriers, or four fifths of all the throat carriers.<sup>30</sup> These figures can be compared with the incidence of nasal carriers of streptococci among hospital admissions for pharyngitis or scarlet fever, which ranged from a quarter to two thirds of the cases.<sup>30, 31</sup>

In view of the obvious importance of the nasal streptococcal disperser, numerous studies were carried out to define more clearly the factors in the individual patient that determined the presence or absence of a profuse growth of streptococci in the nose. It should be emphasized that almost all nasal carriers yield strongly positive pharyngeal cultures. It appears from routine repeated surveys of populations that the nasal carrier state is a far more transient condition than the pharyngeal carrier state, occurring in the first few days or weeks after the patient has acquired a new streptococcal type. Clinical disease may or may not follow the appearance of streptococci in the nose and throat. Occasionally, streptococci have been found only in the nose and not in the throat,<sup>32, 33</sup> but usually within twenty-four to forty-eight hours when the cultures were repeated the throat was positive. The same type of streptococcus is almost always present in both locations. Proliferation of streptococci in the nose may or may not be associated with coryza or symptoms and signs of paranasal sinusitis.

The majority of so-called "healthy carriers" found by surveys gave a history of recent sore throat, cough or nasal discharge, but signs of tonsillitis and sinusitis were not frequent. Many showed a moderate degree of pharyngeal injection, but no reliable distinction could be made at any time on a clinical basis between this group and the non-carriers. Most of the nasal carriers discovered by cultural surveys did not report to sick call at any time, and the rest were usually returned to duty

by the dispensary physician.<sup>22</sup> In spite of the mildness of the signs and symptoms, evidence was obtained of a rising or elevated antistreptolysin titer in 50 to 70 per cent of the ambulatory nasal carriers, and it was concluded that in most cases they represented missed cases of infection rather than true contact carriers with only a symbiotic disease state. It should be emphasized that some of the most "dangerous" of these carriers complained of few symptoms.

Among patients hospitalized with positive nasal cultures the majority had a follicular tonsillitis or severe pharyngitis, and in this group about 60 per cent of cases showed roentgenologic evidence of sinus disease.<sup>20</sup> The streptococcal output, however, did not depend on the presence or absence of sinus involvement, and one must conclude that in many cases marked proliferation of streptococci occurs on the nasal mucosa alone. It seems likely that the development of immunity to the infecting strain can be fairly well correlated with the decline in streptococcal output of many of these carriers and with the gradual return of the nasal mucosa to its normal streptococcus-free state. Within ten days after admission the streptococcal output of 80 per cent of hospitalized nasal carriers fell to low levels, and two months later only 13 per cent of these patients carried any streptococci in the nose, although half were still pharyngeal carriers. Many barracks carriers showed an even shorter duration of the nasal carrier state.

Since the symptoms of the ambulatory nasal carrier may be mild and nonspecific, however great their streptococcal output, their control assumes corresponding importance and difficulty. Cultural surveys, which are the only sure method of selecting these cases out of the herd, may be performed rapidly by the placing of the streakings of nasal swabs from 4 cases on quadrants of a single blood-agar plate. Two to 4 patients can be cultured a minute, depending on the amount of teamwork. Presumptive identification of these cultures is much easier than that of the pharyngeal cultures, especially when large numbers of organisms are recovered.<sup>28</sup>

The chemotherapeutic control of ambulatory nasal carriers has been temporarily successful both with prophylactic doses of sulfadiazine (in the absence of a large proportion of resistant strains) and with calcium penicillin in oil and beeswax (Romansky formula). Sulfadiazine therapy (10 gm daily or more), which clears the nose in two thirds or more of asymptomatic carriers and even in patients may markedly lower the streptococcal output to a safe level, should be carried out for at least three weeks to prevent relapse in many carriers after cessation of therapy. Calcium penicillin given in one dose of 300,000 units a day in oil and wax was found to be much more effective in eradicating streptococci from both the nose and the throat in patients, but half the cases showed a relapse with the same type

after five to seven days of therapy. One quarter of the total again manifested strongly positive nose-blow cultures one to five days after termination of therapy. This period of therapy seems to have been too short for adequate control of patient carriers.<sup>33</sup>

## DISCUSSION

The importance of the nasal carrier of hemolytic streptococci has been referred to by numerous workers in the field of streptococcal epidemiology. Among the first to utilize nasal cultures were Meleney and Stevens,<sup>34</sup> who, in 1926, reported an epidemic of post-operative streptococcal wound sepsis that was traced to the instrument nurse, a nasal carrier. There were several other possible sources for infection from pharyngeal carriers on the surgical staff, but careful serologic analysis utilizing reciprocal agglutination and agglutinin absorption confirmed the identity of one of the wound strains and that isolated from the nurse's nose. In 1933 Colebrook<sup>35</sup> was impressed with the possible role of nasal carriers in the production of puerperal sepsis, because of the increased potentialities for contamination of the hands by handkerchiefs, and cites several cases in which nasal carriers seemed to be the source of infection. Hare,<sup>36</sup> in 1941, first demonstrated that nasal carriers expelled more streptococci than throat carriers, noting in 3 cases that the contamination of the person was more widespread and of longer duration than when only the pharynx was involved. In 1944 Coburn<sup>37</sup> reported two outbreaks of streptococcal disease traceable to post-infection carriers who had clinical and roentgenologic evidence of sinus involvement, nose cultures were not performed. Gordon,<sup>38</sup> in 1932, observed that discharged scarlet-fever patients with rhinitis or sinusitis were more likely to transmit infection than patients without complications, or those with other complications, such as suppurative otitis media. The relative lack of infectivity of simple pharyngeal carriers noted above confirms the conclusions of Bloomfield and Felty,<sup>39</sup> who in 1923 observed the paucity of cross infection between chronic pharyngeal carriers and normal persons rooming together.

The finding that the nasal streptococcal carrier is in most cases an "acute" carrier who has only recently acquired the organism and from whom dispersion of streptococci gradually diminishes as local or general immunity develops re-emphasizes the conclusions drawn by Blake<sup>40</sup> after World War I regarding the importance of acutely infected individuals in the genesis of epidemics. Although Bloomfield and Felty's study emphasized the local parasitism of the tonsil by hemolytic streptococci under conditions of sporadic disease, vast and bitter experience has repeatedly shown that virus diseases affecting the upper respiratory tract, especially influenza and measles, predispose to secondary infection with the streptococcus, which then readily

invades on a wide scale the mucosa of the upper and lower respiratory tract.<sup>41</sup> In view of Glover's<sup>42</sup> production of nasal dispersers of streptococci in ferrets doubly infected with influenza A virus and Group C streptococcus, it would be extremely interesting to know what proportion of acute nasal streptococcal carriers have had their respiratory mucosa already damaged by influenza virus or the virus of the common cold. These ferrets proved highly contagious when placed in close association with other healthy ferrets, and it was shown that administration of streptococci alone infected only the tonsils of the animals, but not the nasal membranes. Infection of the membranes with streptococci was possible only by means of an antecedent or concomitant virus infection.

Since the chemotherapeutic control of nasal dispersers by any means except mass prophylaxis presupposes routine carrier surveys at close intervals (ideally, twice weekly), the use of less cumbersome and protracted safeguards appears to be indicated. Hand contamination from the nose seems to be the most important route of dissemination, and much use could therefore be made of oiling procedures for all handkerchiefs, masks, towelings, bed linen, blankets and clothing with which patients and carriers might come in contact. These procedures have been adapted to standard laundry use and are cheap, nonirritant and safe from fire hazard. The treated textiles cannot be distinguished from those untreated, although the process permanently impregnates woolen fabrics.<sup>43</sup> These oiling procedures have been shown to prevent the major portion of secondary contamination of air and dust resulting from streptococcal carriers.<sup>12</sup> Air disinfection with glycol vapors has been shown to enhance the effect of oiled bedding in reducing streptococcal aërial pollution.<sup>14</sup>

As Hamburger<sup>20, 22</sup> suggests, it seems logical to set up new criteria for the discharge of patients with streptococcal tonsillitis from hospitals, regardless of the presence or absence of a rash. No patient should be discharged who has a strongly positive nasal culture, and all such patients should be carefully isolated or given adequate suppressive chemotherapy. Probably, most patients with only a few colonies in the nose cultures could be discharged after three weeks in the hospital, provided that there were no known susceptibles such as young children or patients with rheumatic fever in the home environment. Proper instruction concerning cleanliness of the hands and disposal of nasal secretion would be an additional safeguard. At least two nose cultures prior to discharge should be obtained, preferably at least forty-eight hours or more after discontinuance of chemotherapy.

There is evidence that other bacteria causing upper respiratory infections are disseminated from the nose in a manner similar to that by which the hemolytic streptococcus is spread. For instance,

nasal diphtheria has been regarded by Place<sup>44</sup> as "by far the most contagious, as discharge through methods and habits of handling may be readily spread about by contact, handkerchiefs, towels, laboratories, candy, toys, hands, garments, etc. Moreover, nasal cases very often escape early detection, under the guise of colds, and allow a longer period of contact than other forms." Localized diphtheria epidemics have been traced to nasal carriers of the same type.<sup>45</sup> Ward and Henderson,<sup>47</sup> in 1907, were not able to control a diphtheria epidemic until they had isolated the nasal as well as the pharyngeal carriers among the population.

Similarly, it is thought that the spread of *Staphylococcus aureus* can best be related to its presence or absence on the nasal mucosa, from which the hands are secondarily contaminated. Miles and his co-workers<sup>48</sup> studied the relation of nasal staphylococcal carriers to wound infection and the bacteriology of the carriers' skins, noting carrier rates of 40 to 50 per cent, with many nasal carriers yielding positive skin cultures. It was possible to prove similarity of types in the nose and on the hands by the phage typing technic in a limited series, and the conclusions were that the hands were the main source for dissemination of coagulase-positive staphylococci from the nose.

Contamination of the hands by staphylococci and streptococci from nasal sources may explain some of the epidemics of food-borne disease caused by these organisms reported from military and civilian sources in the past few years.<sup>49</sup> It is well to remember that organisms from the upper respiratory tract of food handlers may be just as dangerous as intestinal pathogens when opportunity occurs for food contamination, and, in addition, much of the intra-familial spread of beta-hemolytic streptococci may occur by this route.<sup>10</sup> Transmission of streptococci by hand-to-mouth contamination (or via fomites) seems to be particularly important in children. As a result of observations on the inadequate sterilization of mess kits during the influenza pandemic of 1918-1919, Cumming and Spruit<sup>51</sup> stressed the significance of streptococci and pneumococci on the hands and in the wash water in explaining the high incidence of secondary bacterial infection among troops in World War I. They noted beta-hemolytic streptococci in the mess-kit wash water in 84 per cent of examinations and on the hands of 38 per cent of military personnel. Their studies, which included observations on the experimental transmission of mouth-inoculated *Serratia marcescens*, tended to show a lower incidence of pharyngeal streptococcal carriers and a reduced incidence of influenza and measles among troops boiling all their mess gear as contrasted with a carefully selected control group with inadequate wash-water temperatures.<sup>52</sup> It is well to recall these studies to emphasize the varied routes that upper respiratory pathogens may take in passing from person to person.



Finally, it should be remembered that the simple pharyngeal carrier of beta-hemolytic streptococci always represents a hazard to his fellows, different from that arising from a nasal carrier only in degree. Much of the sporadic transfer of streptococci probably takes place chiefly from the pharyngeal carriers, as the very low incidence of nasal carriers under these conditions attests.

### SUMMARY

There is at present ample evidence that the "strongly positive" nasal carrier of beta-hemolytic streptococci disperses approximately one hundred times the number of organisms to his environment as the pharyngeal carrier, irrespective of the presence of a rash or the severity of the symptomatology. Most of the nasal carriers represent cases of streptococcal infection in the acute phase so far as can be determined by clinical and immunologic evidence, although in many cases symptoms are so mild that they are overlooked or neglected. Probably less than 10 per cent of these carriers continue to disperse large numbers of streptococci for periods longer than two or three weeks. Such carriers as these, however, may initiate localized outbreaks of streptococcal disease, and when acute nasal carriers are multiplied as a result of cross infection, the incidence of clinical disease will rise sharply, with a secondary rise in the pharyngeal carrier rate representing contact carriers and convalescent cases with persistent parasitism and slight potentiality for production of secondary cases. Widespread and lasting control of the proliferation of streptococci on the nasal mucosa is one of the chief problems in the prevention of epidemic streptococcal disease today.

Chemotherapy with sulfadiazine (in the absence of resistant strains) or penicillin, newer technics of environmental dust control with oil and air sanitation using germicidal vapors have been shown to have definite value in reducing possibilities for cross infection offered by nasal streptococcal dispersers.

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## CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C CABOT

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### CASE 33521

#### PRESENTATION OF CASE

A fifty-year-old woman was admitted to the hospital because of abdominal pain.

One week before entry, two hours after a normal bowel movement, the patient was suddenly seized with severe persistent lower abdominal crampy pain, and a few hours later she began to vomit. A physician gave her some pills, following which she passed some gas, but the pain persisted throughout the abdomen and she continued to vomit. She was then taken to another hospital, where a Miller-Abbott tube was passed. This lessened the distention, and she stopped vomiting.

Twenty-three years before entry and again three years later, the patient had full-term normal deliveries but had had a great deal of pain throughout both pregnancies. For this reason she was sterilized six years after the last pregnancy by the removal of the tubes and one ovary, the appendix was also removed. The menopause occurred nine months before admission, and she had subsequently had only intermittent bleeding.

Physical examination revealed a slightly distended "doughy" abdomen with active peristalsis. There was a freely movable, nontender golfball sized mass in the left midabdomen. Vomiting had ceased. She passed gas by rectum, and an enema gave good results.

The temperature was 98°F, the pulse 90, and the respirations 22. The blood pressure was 118 systolic, 70 diastolic.

The red-cell count was 4,660,000, with a hemoglobin of 11.4 gm and a hematocrit of 39 per cent.

The white-cell count was 11,200, with 87 per cent neutrophils. The serum chloride was 85 milliequiv per liter. The serum protein, the nonprotein nitrogen, the fasting blood sugar and the prothrombin time were within normal limits.

An x-ray film showed the tip of the Miller-Abbott tube in the left midabdomen, with dilated loops of small bowel both proximal and distal to the tip.

The day after admission the dilated loops proximal to the tube were no longer visible, whereas those in the right lower quadrant close to the cecum persisted. On the third day the tip of the Miller-Abbott tube was still in the same position. Injection of 50 cc of barium through the tube revealed knuckling and narrowing of the small bowel to a width of 1.0 cm or less. There was no evidence of prominence of the mucosa. The loops of bowel immediately proximal and distal to the tip were not dilated. A film taken four hours later showed the barium to have stopped in the same loops, and the persistent dilated loops of small bowel were noted in the right side of the abdomen.

The patient was treated with Amigen, vitamin B<sub>12</sub>, hykinone and intravenous 5 per cent dextrose in saline solution. The chloride increased to 94 milliequiv per liter, and the hematocrit and hemoglobin were reduced to 34 per cent and 9.4 gm respectively.

An operation was performed on the third hospital day.

#### DIFFERENTIAL DIAGNOSIS

DR. CLAUDE E. WELCH: This is an obvious case of intestinal obstruction. One of our major problems is to determine the site of the obstruction. Clinically the best clue is the location of the pain. The patient had severe lower abdominal crampy pain, which usually means that the colon is involved rather than the small bowel. However, when a patient begins to vomit shortly after the attack of cramps, obstruction is presumed to be in the small bowel rather than the large, and the repeated vomiting is evidence more in favor of small-bowel than large-bowel obstruction. Since the character of the pain during the pregnancies is not described I am unable to make much out of this symptom.

"She was sterilized six years after the last pregnancy by the removal of the tubes and one ovary." This might suggest, is an unusual method of sterilization, and implies that there was something

wrong with the pelvic organs at that time requiring removal of the ovary

"The menopause occurred nine months before admission, and she had subsequently had only intermittent bleeding" That is a confusing statement, and is impossible to interpret

One should pay attention to masses, even though they are very small, but because of its character I shall say that this so-called mass was the distended balloon of the Miller-Abbott tube I may be wrong, but it seems to fit better with the history

There is no note of vaginal or rectal examinations In trying to abstract some of these histories it is difficult not to leave out some of the important points, but I think that we are justified in assuming that those examinations were made and were negative

The blood studies showed evidence of dehydration as brought out in the latter part of the record There was a slight leukocytosis, with an increase of neutrophils, but not enough to be of great significance The serum chloride was low because of the repeated vomiting It would have been interesting to know whether the stool that was obtained by enema was guaiac positive or negative That specimen probably eluded the watchful eye of the nurse on the ward and was disposed of before it reached the laboratory

May we see the x-ray films?

DR STANLEY M WYMAN The first examination shows dilated loops of small bowel assuming a lace pattern There is some barium remaining in the colon from a previous examination, and there is gas extending up to the region of the splenic flexure The film taken the next day shows some decrease in distention of the small bowel, but the tip of the Miller-Abbott tube is not changed in position The position of the tube is constant throughout the series of films Two days after the first film barium was introduced into the Miller-Abbott tube, and the spot films taken at the time of examination show the tip of the tube in the apparent area of narrowing at this point in the small bowel It is rather hard to interpret this without having done the examination There is no definite evidence of a change in the mucosal pattern This is a loop of dilated small bowel just distal to the tube, so that there is at least one point of narrowing in the small bowel without apparent involvement of the mucosa

DR WELCH Do you see any evidence of air in the liver radicles?

DR WYMAN There is no evidence that I can see of gas extending up into the liver shadow

DR WELCH You can see nothing that suggests a shadow of calcium rather than barium in the lower bowel?

DR WYMAN I do not see any stones scattered through the abdomen I think that there is at least

one point of narrowing in the small bowel that does not involve the mucosa, so far as I can tell

DR WELCH The x-ray examination has been very helpful in many respects. Even if he had done the examination, I imagine that Dr Wyman would agree that it would be difficult to interpret the spot films

When faced with a case of intestinal obstruction, the surgeon must attempt to be more specific and attempt to name the causative factor of the obstruction The first question is to determine whether the large bowel or the small bowel is involved In this case the x-ray examination has been of great value because the barium studies have shown a fairly normal colon with no distention, indicating that the lesion involves the small intestine The surgeon must next determine whether a strangulating or a nonstrangulating obstruction is present Strangulating obstruction is identified by the presence of tenderness, by the absence of peristalsis and often by leukocytosis A patient with this type of obstruction must be operated on promptly. Obviously, a strangulating obstruction was not present in this case, so that we immediately rule out the strangulating lesions of the small bowel producing obstruction, which include intussusception, mesenteric thrombosis and volvulus Consequently, we pass on to the nonstrangulating types To begin with, there are a few rather unlikely lesions of the small bowel that can be excluded immediately It is unlikely that this patient had an inflammatory lesion of the distal ileum I assume that the statement in the x-ray interpretation that there was evidence of prominence of the mucosa is meant to indicate no evidence of regional ileitis Is that correct?

DR WYMAN I should think so.

DR WELCH It would be unusual for regional ileitis to appear with the first symptoms at fifty years of age and then with acute obstruction The same statement is true of other types of inflammatory diseases in the distal ileum What, then, are the common and likely causes of the obstruction in this patient? If one can judge by percentage figures, hernia, either obvious or concealed, should be the most obvious choice A careful examination was made of this woman, and the chances that a hernia was undiscovered are rather slight A femoral hernia is often hard to find and may be overlooked However, that is unlikely In the presence of operative scars, bands or adhesions furnish by far the most frequent causes of intestinal obstruction and, until we can discover a better cause, must be considered seriously

The next thing to be considered is a foreign body In this part of the country, where persimmons are not a favorite part of the diet, the only foreign body that commonly obstructs the small bowel is a gallstone That is a difficult diagnosis to make, especially in the absence of signs pointing to the gall bladder There was no gas in the biliary radicles and no evidence of stone by x-ray examination

The third most probable cause to be considered is that of tumor involving the bowel. It is unlikely that this was a primary carcinoma of the ileum. The obstruction came on suddenly, and there was no evidence of bleeding by rectum. Our attention has been called to a mass, and that might be interpreted as tumor of the small bowel. I believe that we have a much better right to call it a distended Miller-Abbott tube. Could this have been one of the peculiar benign tumors of the lower portion of the small bowel, such as carcinoid? Again, there is no evidence in its favor, its rarity rules this diagnosis out as a likely possibility.

Could the patient have had metastatic carcinoma arising somewhere in the abdomen and involving the terminal portion of the small bowel, especially at the multiple points of obstruction suggested by x-ray study? It is possible, but again in a woman the usual source of such a carcinoma is in the ovary and we have the right to assume that the pelvic examination had been negative.

Since we have to make a diagnosis in this case of intestinal obstruction, I believe that it is obstruction of the small bowel, in the lower ileum, nonstrangulating in type, due to bands from the previous operation.

#### CLINICAL DIAGNOSIS

Intestinal obstruction

#### DR. WELCH'S DIAGNOSIS

Intestinal obstruction, due to adhesive bands

#### ANATOMICAL DIAGNOSES

*Acute oophoritis and perioophoritis*

Intestinal obstruction, due to inflammatory adhesions

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY. I am sorry that the surgeon who operated on this woman is not present to discuss the diagnostic problem. So far as the record is concerned he did not commit himself beyond the diagnosis of intestinal obstruction.

The patient was explored, and several coils of small bowel were found adherent to a mass lying at the brim of the pelvis. The adhesions were fibrous, and it was possible to separate them with blunt dissection. When that was done, it was found that the mass was a considerably enlarged ovary measuring 7 cm in diameter, the center of which was filled with pus. The ovary was removed, and following operation the patient made a rapid convalescence. Inasmuch as the uterus and both tubes had been removed fourteen years before, I believe that we are safe in assuming that this was a hematogenous infection of the ovary.

#### CASE 33522

#### PRESENTATION OF CASE

*First admission.* A fifty-one-year-old housewife was admitted to the hospital because of shortness of breath.

Twenty-nine years before entry she had an attack of rheumatic fever characterized by pain and swelling of the wrists and hands. She was put to bed for three months. After this she felt well and had two children. She was told, however, that her heart was weak, and eighteen years before entry her last pregnancy was terminated for this reason. Two years before entry she began to have dyspnea on exertion, requiring bed rest occasionally for a day or two. Recently she had to use two pillows at night. Two weeks before entry she "contracted a cold" with cough and daily expectoration of several tablespoonfuls of foamy, sometimes blood-stained sputum. She became extremely dyspneic and orthopneic, and was treated with digitalis, Mercupurin and penicillin with doubtful improvement. On the night before admission she became worse, with severe cough and orthopnea.

Physical examination revealed an orthopneic woman, with some cyanosis and malar flush. The neck veins were distended and pulsating. There were basal rales on both sides of the chest. An examination of the heart was reported as follows:

The heart is tremendously enlarged to the left and right, with the point of maximal impulse and left border of dullness at the anterior axillary line in the fifth interspace. There is enlargement to the right in the fifth space, with the right border of dullness 5 cm. from the midsternal line. There are sounds of good quality. The mitral first sound is strong and booming, and the pulmonic second sound is very much increased and duplicated. At the apex there are Grade IV systolic and diastolic murmurs with an accompanying thrill. The systolic murmur is loud and harsh through all of systole and is transmitted to the back. The diastolic murmur is very loud and low pitched and occupies all of diastole, with the strongest element in mid diastole. In the right lower portion of the chest anteriorly, over the upper border of the liver, there is a very loud Grade III or IV rough systolic murmur with a thrill. At the base no murmurs that can be separated from the widely transmitted ones noted above can be made out. The rhythm is totally irregular.

The liver edge was palpated 10 cm. below the costal margin and was firm. The spleen was felt 2 cm. below the costal margin. No abdominal fluid was detected. There was only minimal pitting edema of the ankles.

The temperature was 101.4°F, and the pulse 96. The blood pressure was 120 systolic, 80 diastolic.

An electrocardiogram showed auricular fibrillation, the ventricular rate averaging 100. The QRS complex was 0.09 second, with normal voltage, right-axis deviation, absent R<sub>s</sub>, prominent QS and very low T waves in Lead 1, sagging ST segments in Leads 1, 2 and 3, slightly inverted T waves in Lead 3, small R and prominent S waves in

Leads CF<sub>1</sub> and CF<sub>2</sub> and upright T waves in Leads CF<sub>3</sub>, CF<sub>4</sub> and CF<sub>5</sub>. There was one ectopic ventricular beat.

X-ray examination of the chest revealed that the heart was enormously enlarged in all directions, the transverse diameter being 22 cm and the chest 25.5 cm. There was calcification of the arch of the aorta. The left auricle appeared extremely large, pressing on the left main bronchus and compressing



FIGURE 1

it posteriorly. There was fluid in both pleural cavities. The hilar shadows were prominent (Fig. 1).

Examination of the blood disclosed a hemoglobin of 14 gm and a white-cell count of 12,000, with 90 per cent neutrophils. The sedimentation rate was 14 mm in 1 hour (corrected). The prothrombin time was normal. The van den Bergh reaction was 0.8 mg per 100 cc direct and 1.4 mg indirect. The cephalin-flocculation test was +++ in forty-eight hours. The urine showed a + test for albumin, with an occasional hyaline cast in the sediment. The stools were guaiac negative.

The patient was treated with penicillin, a low-sodium diet, ammonium chloride and Purodigin. She had an episode of severe dyspnea and pain in the right side of the chest the day after admission. Following this her condition improved steadily. The temperature, pulse and respirations were normal, and the chest rales cleared. After two weeks she was discharged to a nursing home on a maintenance dose of Purodigin.

*Second admission* (five weeks later). The patient was readmitted because of severe dyspnea and chest pain. In the interval she had stayed in bed most of

the time. For two weeks prior to readmission she had sharp pains in the right axilla, aggravated by cough and respiration. On the day before readmission she had a "cold," and around supper time, she suddenly developed a persistent cough and foamy, white sputum. The dyspnea and pain in the right side of the chest became very severe, and she had to sit up in bed all night. By morning she felt feverish and had noticed some blood staining of the sputum.

Physical examination revealed dyspnea, cyanosis and cough. The temperature was 103°F. There were rales in both sides of the chest but no signs of consolidation or fluid. There was a transient friction rub in the left axilla. The heart signs were the same as on the previous admission. The rate was irregular with a pulse of 90 and a blood pressure of 115 to 120 systolic, 70 to 80 diastolic. The liver edge was palpated four fingerbreadths below the costal margin and was pulsating. There was shifting dullness in the flanks and bilateral ankle edema, more on the right side. There was no calf tenderness or pain on dorsiflexion.

Examination of the blood disclosed a red-cell count of 4,100,000, with a hemoglobin of 14 gm, and a white-cell count of 8200, with 88 per cent neutrophils. The urine showed a specific gravity of 1.018, with a ++ test for albumin. The sputum was negative for pneumococci. An electrocardiogram was similar to that on the previous admission.

A bilateral femoral-vein ligation was done on the second hospital day. The congestive failure rapidly subsided with digitalis and Mercupurin, and after the fifth hospital day, the temperature remained normal. The patient was discharged at the end of two weeks on a low-sodium diet, digitalis, ammonium chloride and Aminophylline suppositories.

*Third admission* (five weeks later). The patient returned to the hospital because of an incarcerated femoral hernia. A herniorrhaphy was done, and 13 cm of infarcted ileum was resected. She made a good recovery and was discharged eighteen days later on a regime of digitalis, ammonium chloride, a low-sodium diet and mercurhydriin intramuscularly.

*Fourth admission* (six weeks later). Because of the gradual onset of additional symptoms of feverishness, night sweats, shoulder pains and malaise, the patient was readmitted. There were no chest, abdominal or back pains, gross hematuria, chills, pains in the fingertips or petechiae.

The physical examination was essentially similar to that on previous admissions except that the examiner noted systolic murmurs at the base on each side of the sternum, in addition to the apical murmurs and those in the right side of the chest. The spleen was firm, tender and palpable 3 cm below the costal margin. There was only slight ankle edema.

The temperature was 100°F.

An x-ray film of the chest revealed some fluid in the right pleural sinus. The electrocardiogram was unchanged.

The hemoglobin was reduced to 10 gm. The red-cell count was 3,000,000, and the white-cell count was 7100. A cephalin-flocculation test was +++ in twenty-four and forty-eight hours, and the brom-sulfalein test showed only 4 per cent retention of the dye. Repeated blood cultures were negative. The urine gave a + test for albumin.

The patient was hospitalized for sixteen days and during that time the temperature ranged from 98° to 100°F, the pulse from 70 to 80, and the respirations from 20 to 30.

**Final admission** (eight weeks later) The patient had been reasonably well until the midnight before entry, when she complained to her daughter that she felt as though the blood were rushing to her head, and asked to go to the bathroom. The daughter helped her to the bathroom, and on returning the patient rather suddenly became severely short of breath and cyanotic and was unable to speak. There was no unconsciousness, convulsive movements or incontinence.

Physical examination revealed a cyanotic, dyspneic, slightly confused woman with a temperature of 100°F. The neck veins were distended and pulsating. The heart was fibrillating at a rate of 95 per minute (apical), and the blood pressure was 150 systolic, 90 diastolic. The lungs were resonant throughout. The respiratory sounds were faint, and there were tight expiratory wheezes over the entire chest. There were moist inspiratory rales at both bases, more on the right. The liver edge was palpated three to four fingerbreadths below the costal margin and was firm and sharp. The spleen was not felt. There was a +++ pitting edema of both ankles. There was flaccid paralysis of the right lower part of the face and the right arm and leg, as well as questionable aphasia. The deep tendon reflexes were equal on both sides. Babinski and Chaddock signs were suggestive on the right. The neck was not stiff.

The white-cell count was 7100, with 83 per cent neutrophils. The hemoglobin was 11 gm. The urine showed a ++ test for albumin. The cerebrospinal fluid contained 200 red cells per cubic millimeter in one tube and 500 red cells in the other.

The patient was given oxygen, Cedilamid and mercuranthin. The next day she developed dullness and almost absent breath sounds in the right middle and lower lobes, and the white-cell count increased to 16,100. An emergency bronchoscopy was done, and this increased the breath sounds and aeration temporarily although an obvious plug of secretion was not removed. Tracheal rales were soon heard over the entire chest. She became exhausted and unresponsive and died quietly two days after admission.

## DIFFERENTIAL DIAGNOSIS

**DR OGLESBY PAUL** May we start by seeing the x-ray films?

**DR STANLEY M WYMAN** The huge heart described is seen to be essentially unchanged from the first observation until six months later. It is enlarged both to the right and to the left, the greater enlargement seems to be toward the right. There is a small quantity of fluid in both pleural spaces. The left oblique view shows the left main bronchus elevated, compressed and narrowed by what I take to be a huge left auricle. The right oblique view again shows a large left auricle. There is calcification of the aortic arch well over to the right. No note is made by fluoroscopy of calcification in the heart itself. I cannot see any on the film. Later films show the fluid in the right pleural space to have increased considerably five months after the first film. There is no very good evidence of enlargement of the region of the left ventricle.

**DR PAUL** It would be very hard to make a diagnosis of pulmonary infarction with a heart of that size, would it not?

**DR WYMAN** Yes.

**DR PAUL** Starting with the first admission, we have no reason to question the fact that this patient had had rheumatic fever in the past leading to severe rheumatic heart disease. The question is, What had changed the course from one of fairly good tolerance of effort to one of sudden appearance of congestive failure? Several things should be considered. She may have developed auricular fibrillation or flutter, or she may have had a reactivation of rheumatic fever or developed some other infection, perhaps even bacterial endocarditis. A third possibility is that of pulmonary infarction. It is interesting that when she came in, she was in severe failure. The murmurs can be interpreted as indicating mitral stenosis and marked mitral regurgitation; the question arises, What was the murmur in the right lower portion of the chest anteriorly over the liver area? That may have been the murmur of mitral regurgitation well heard in the right side of the chest because the left auricle extended so prominently to the right. Ordinarily, I suspect that it is better heard posteriorly and in the axilla than anteriorly. A less likely possibility is that it represented the murmur of aortic stenosis. The splenic enlargement does not necessitate a diagnosis other than rheumatic heart disease and congestive failure. Occasionally, we see patients in congestive failure who do have palpable spleens, without other evidence of bacterial endocarditis. It should raise the possibility of bacterial endocarditis but does not necessitate making that diagnosis.

The electrocardiogram is consistent with mitral stenosis. The absence of apemias on the first admission is of course some evidence against rheumatic and bacterial endocarditis. The patient

was considered on the first admission to have infection, not rheumatic in type, for she was given penicillin and did improve. It seems probable in view of the second admission that she actually had repeated episodes of pulmonary infarction, and following ligation of the femoral veins bilaterally she appears to have done well for a time.

The first two admissions may therefore be explained on the basis of severe rheumatic heart disease complicated by multiple pulmonary emboli.

We do not need to go into the third admission, when a herniorrhaphy was performed, except to say that despite marked valvular disease, the patient showed good tolerance for major surgery. Nothing else is indicated in that note to show any new findings.

The fourth admission is interesting. For the first time the patient complained of persistent fever, sweats and general malaise, and for the first time she was anemic. When she was admitted, she showed less evidence of failure than she had on previous admissions, and had no leukocytosis. There were no positive joint findings, although it is stated that there were joint pains, and no nodules, petechiae, clubbing of the fingers or weight loss were mentioned. The pulse was not rapid. It is stated that repeated blood cultures were negative. She was in the hospital for sixteen days, so that there was a considerable period in which cultures could have been taken, apparently, they were negative or showed only contamination.

She was sent home, presumably with a diagnosis of active rheumatic fever. I should think that she would not have been sent home had bacterial endocarditis been seriously considered. No mention of treatment is made, but I gather that there was no other evidence of infection suggesting the need for chemotherapy.

She did reasonably well during the intervening eight weeks. "Reasonably well" is to my mind a tribute to her heart, for with a heart of this size one would hardly expect the patient to do well, especially in view of the fact that in the previous six months, she had had four hospital admissions, two operations and repeated pulmonary emboli. The fact that she did reasonably well suggests that there was no serious infection, particularly bacterial endocarditis. There is no mention of new symptoms.

Finally, she turned up in the hospital for two days with a terminal cerebrovascular accident of some type. Again, at this final admission we are not told that examination showed clubbing or petechiae or enlargement of the spleen. The anemia was, if anything, less than before. (Perhaps the patient was dehydrated.) Certainly, it does not appear that she was more anemic. She finally succumbed with pulmonary complications due to plugging of the right main bronchus.

I believe that the diagnoses until the fourth admission were rheumatic heart disease, mitral stenosis

and regurgitation, possibly involvement of the aortic valve, quite possibly a functional tricuspid regurgitation and old pulmonary infarction. The question now arises, Was the fourth admission related to the final admission when she succumbed? It may have been, for she may have had subacute bacterial endocarditis on both occasions. A diagnosis of active rheumatic fever on the fourth admission and then bland embolism on the final admission do not necessarily bear any relation, however. So far as I know, there is no correlation between rheumatic activity and the incidence of fatal or nonfatal emboli from the left or right auricle.

What is in favor of subacute bacterial endocarditis? The history is classic feverishness, sweats and malaise occurring insidiously, low-grade fever and joint pains (which raise the possibility of associated active rheumatic fever). Joint pains of a vague type are at times described in subacute bacterial endocarditis without other clear evidence of rheumatic activity. The spleen was palpable, and there was a new murmur, as well as a basal systolic murmur not previously mentioned. It is possible that the murmur was a transmission from the Grade IV murmur described at the apex—it was loud enough to have been heard at the base. The absence of leukocytosis is not unusual in bacterial endocarditis. Finally, one could explain the terminal episode as representing the tossing off of an embolus from the vegetations in the heart. There are certain things against that diagnosis, however. The first and most important is that during the eight-week period in which the patient went home following the fourth admission, she apparently did quite well. I believe that if she had had bacterial endocarditis, she would have had a downhill course, at least sufficiently obvious to have deserved reference to symptomatology. I also believe that she would have become more anemic rather than having the blood improve to the extent that it did. Repeated blood cultures were negative. Also on the final admission, the spleen was not palpable and appears to have grown somewhat in size rather than diminished. No weight loss is noted in the history, and there was no clubbing of the fingers. Also somewhat against the diagnosis of bacterial endocarditis is the fact that the patient had marked valvular disease. We more commonly associate bacterial endocarditis with moderate or mild valvular disease than with severe valvular disease. Finally, the combination of auricular fibrillation and bacterial endocarditis in the same patient is not common.

A few remarks about rheumatic fever itself are indicated. She was a known rheumatic patient, and rheumatic activity in an adult is probably more frequent than we appreciate. She did have a low-grade fever, of the type one expects more in rheumatic fever than with subacute bacterial endocarditis. She had joint pains and anemia. She also

improved to some extent in the hospital without chemotherapy, for she was sent home. I would not expect her to have improved significantly on bed rest if she had had bacterial endocarditis. To explain the terminal episode, we must assume that she had an embolus from the left auricle, which was not related to the presence of active rheumatic fever.

On reviewing the evidence I should say that we have more against the diagnosis of bacterial endocarditis than for it. I should like therefore to make a diagnosis of chronic rheumatic heart disease, with mitral regurgitation and mitral stenosis. The patient may have had aortic disease, but I cannot be sure from the evidence at hand. I would not be surprised if a functional tricuspid insufficiency was indicated by the presence of a dilated tricuspid ring, and believe her heart to have been large, with a big left auricle and evidence of old pulmonary infarcts, which may have been found as healed scars at post-mortem examination. I suspect that she had a terminal embolus from the left auricle to the left cerebral hemisphere. I think that subacute bacterial endocarditis is less likely and shall put it as my second choice.

DR. HOWARD B. SPRAGUE: Would you entertain the possibility of adding an interauricular septal defect to explain the fact that she did so well for so long and also to explain the somewhat abnormal transmission of murmurs?

DR. PAUL: I should think the course was consistent with severe rheumatic heart disease alone. The murmurs themselves were probably consistent with that diagnosis.

#### CLINICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and regurgitation  
Embolism of left middle cerebral artery

#### DR. PAUL'S DIAGNOSES

Rheumatic heart disease, with mitral stenosis and regurgitation  
Rheumatic endocarditis, chronic, aortic?  
Cardiac hypertrophy and dilatation, especially left auricle  
Mural thrombus, left auricle  
Pulmonary infarcts, healed  
Cerebral embolus  
Subacute bacterial endocarditis?  
Chronic passive congestion of spleen

#### ANATOMICAL DIAGNOSES

Rheumatic heart disease, with mitral stenosis and insufficiency  
Mural thrombus, left auricle  
Cerebral embolus, left middle cerebral artery  
Endocarditis, chronic rheumatic, slight, aortic and tricuspid  
Cardiac hypertrophy and dilatation, especially left auricle  
Rheumatic endocarditis, chronic, aortic  
Chronic passive congestion of spleen and liver  
Renal infarcts, healed

#### PATHOLOGICAL DISCUSSION

DR. TRACY B. MALLORY: At post-mortem examination the heart was enormously dilated but not very much hypertrophied, it weighed 400 gm., which is perhaps 30 per cent above normal for a woman of this size. The cavity of the various chambers was estimated to contain about 100 cc. on the left and 200 cc. on the right, the right auricle contained 300 cc., and the left auricle 1000 cc. The mitral valve was severely stenotic and also probably showed regurgitation. There were only traces of rheumatic involvement on the aortic and tricuspid valves. I should think it doubtful if either of them was functionally inadequate. The lungs revealed comparatively little evidence of chronic passive congestion. There was a scar of an old pulmonary infarct of considerable size. The kidneys likewise showed scars of old healed infarcts, and there was a fresh embolus in the middle cerebral artery, with softening of the left cerebral hemisphere. The source of the embolus was a large thrombus in the enormously dilated left auricle.

DR. RICHARD J. CLARK: What was the size of the spleen?

DR. MALLORY: It weighed 275 gm. That is about an average weight for the spleen of chronic passive congestion and rheumatic heart disease. I doubt if it could have been palpated as described in the record. It is rare that a spleen less than 400 gm. can be felt.

DR. CLARK: Was there any positive evidence of active rheumatic infection?

DR. MALLORY: None whatever, grossly or microscopically.



income Some fellows may mistakenly believe that with the additional increase from the Massachusetts Medical Society members their dues will no longer be required The combined income from the Library's investments and dues and the Massachusetts Medical Society members will just about carry the contemplated increase in services, leaving nothing over for the very necessary completion of seven unfinished tiers of stacks, the refurnishing of Holmes, Sprague and Ware halls and the completion of the also unfinished Periodical Room If money is borrowed for these structural changes (and they are necessary if the Library is to fulfill its mission) it is evident that not only all this income but more will be necessary It follows, then, not only that all fellows must retain their membership but also that more must be acquired

The fellows constitute the legal corporation of the Library, control its assets and real estate and elect its officers When funds are obtained to refurnish parts of the building it is planned to set aside certain rooms for the exclusive use of the fellows To be a fellow of the Boston Medical Library will continue to be a real distinction

### SUBSCRIPTION RATE INCREASES

The *New England Journal of Medicine*, after twenty-seven years without an increase in subscription rate, finds it necessary at last to pass on to its subscribers part of the growing cost of publication After January 1, 1948, the regular subscription rate will be \$7 00 per annum

### MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

#### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

CLINIC	DATE	CLINIC CONSULTANT
Salem	January 5	Paul W Hugenberger
Haverhill	January 7	William T Green
Brockton	January 8	George W Van Gorder
Lowell	January 9	Albert H Brewster
Greenfield	January 12	Charles L Sturdevant
Gardner	January 13	Carter R Rowe
Worcester	January 16	John W O'Meara
Fall River	January 19	David S Grice
Springfield	January 20	Garry deN Hough, Jr
Pittsfield	January 21	Frank A Slowick
Hyannis	January 22	Paul L Norton

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments Patients are seen by appointment only

### NOTICES

#### JOSEPH H PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston  
Lecture Hall, 9-10 a m

#### MEDICAL CONFERENCE PROGRAM

- Wednesday, January 7 — Histochemical Studies of Blood and Bone Marrow Dr Jack Rheingold  
Friday, January 9 — Carcinoma of the Prostate Dr George G Smith  
Wednesday, January 14 — Pediatric Clinicopathological Conference Drs James M Baty and H E MacMahon  
Friday, January 16 — Diagnosis of Thyroid Deficiency and the Use of Thyroid Hormone Therapy in Infants, Children and Adolescents Dr Nathan B Talbot  
Wednesday, January 21 — Recurrent Spontaneous Pneumothoraces and Their Surgical Treatment Dr Francis M Woods  
Friday, January 23 — Rheumatic Fever from the Epidemiological and Preventive Points of View Dr David D Rutstein  
Wednesday, January 28 — The Tuberculoid Structure. Dr Francis M Thurmon  
Friday, January 30 — The Clinical Significance of Various Types of Peripheral Neuritis Dr D Denny-Brown  
On Tuesday and Thursday mornings from 9 00 to 10 00, Dr S J Thannhauser will give medical clinics on hospital cases On the second and fourth Friday afternoons of each month, therapeutic conferences will be held from 2-00 to 4 00 with round-table discussion, Dr R P McCombs, moderator, Dr Merrill Sosman will conduct x-ray conferences from 4 00 to 6 00 On Saturday mornings from 9 00 to 10 00 clinics will be given by Dr William Dameshek Medical rounds are conducted each weekday except Saturday by members of the staff from 12 00 to 1 00  
All exercises are open to the medical profession

### TUFTS ALPHA OMEGA ALPHA

The Tufts chapter of the Alpha Omega Alpha will meet at the Boston Medical Library, 8 Fenway, on Wednesday, January 7, at 8 p m Dr Siegfried J Thannhauser and Dr H Edward MacMahon will conduct a clinicopathological conference

### NEW ENGLAND HOSPITAL FOR WOMEN AND CHILDREN

The monthly clinical conference and meeting of the staff of the New England Hospital for Women and Children will be held on Thursday, January 8, at 7 15 p m in the classroom of the Nurses' Residence The subject, "Subarachnoid Hemorrhage," with a case presentation, will be discussed by Dr Edith D Stanley Dr Eleanor E Cowan will be chairman Since this is the annual meeting, a full attendance is requested The change of date from January 1 to January 8 should be noted

### CONFERENCE ON NORMAL AND PATHOLOGIC PHYSIOLOGY OF PREGNANCY

The Committee on Human Reproductive Research Council, in behalf of the National Maternal Health, will sponsor a conference on normal and pathologic physiology of pregnancy Dr Earl T Engle, assisted by the National Research Council sessions will be held at the Hotel 30 and 31

Among those participating in Arthur T Hertz, Don Wayne Smith and Foster Kellogg and

(Notices continue)

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### KEY TO ABBREVIATIONS

c — correspondence  
cr — case record  
e — editoria  
ma — medicolegal abstract

mdph — Massachusetts Department of Public Health  
masa — Massachusetts Medical Society  
mp — medical progress  
misc — miscellany  
mr — meeting report

n — notice  
nms — New England Surgical Society  
o — obituary  
— original article

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CASE RECORDS  
OF THE MASSACHUSETTS GENERAL HOSPITAL

WEEKLY CLINICOPATHOLOGICAL EXERCISES

FOUNDED BY RICHARD C CABOT

TRACY B MALLORY M.D. *Editor*  
BENJAMIN CASTLEMAN M.D. *Associate Editor*  
EDITH E. PARRIS *Assistant Editor*

VOLUME 33

1947

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1947

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